CONDENSATION OF ALDEHYDES WITH AMIDES

Part XII. Condensation of Benzaldehyde and o-Chlorobenzaldehyde

By Gur Saran Bhatnagar and Kantilal C. Pandya

(St. John's College, Chemistry Laboratory, Agra)

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Pandya and Miss Pandya have shown that the aldehyde-malonic acid condensation is very favourably influenced by a chlorine or a bromine atom on the ring of the aldehyde. In the present paper an effort is made to find out if the aldehyde-amide condensation is similarly influenced by one chlorine atom on the aromatic ring of the aldehyde. In order to make the comparison good it was necessary to have definite yields from the benzaldehyde-amide condensation. While this condensation, using benzaldehyde and various amides, has been studied by a host of workers in the past sixty years, the study has been carried out under very different conditions and in many cases the yields are not to be found. In the present investigation, therefore, it was necessary to have the figures of the yields of the condensations of benzaldehyde with various amides employing the same method that might be used for the chloro-benzaldehydes. Some of these benzylidene-amides have been well known: others described here have been obtained for the first time.

Chlorine is found, on the whole, to increase the yield of the condensation product, though not in all cases. The conclusion has to be also limited by the fact that only the o-chlorobenzaldehyde has been studied here, the m- and the p-ones being not available at the moment.

In the condensations reported in the earlier eleven papers, it was found that heating the aldehyde and the amide alone together was one of the best of the processes: in some cases, however, the yields were distinctly improved by the use of 0.1-0.15 mol. of pyridine, though this was not so in all the cases examined. Here also pyridine has been found to improve the yield by 1 to 5%: but temperature and the time of heating had a more pronounced effect.

The products have generally been of the benzylidene-bisamide type, though, in the earlier papers, the monoamides too have been met with. The aldol that must have presumably preceded the monoamide, has not so
far been obtained by any worker. Both benzaldehyde and o-chlorobenzaldehyde gave bisamide products. Formamide presented the usual difficulty, giving only a 13% yield with benzaldehyde. Another worker here (Mr. K. K. Baslas) had obtained a 36% yield in 1942.3

EXPERIMENTAL

Condensation of Benzaldehyde with Amides

With Benzamide

Roth's4 experiment as well as that of Hoffmann and Victor Meyer,5 namely that of heating the aldehyde and the amide alone was first repeated.

i. In the Absence of Pyridine or any Condensing Agent.—0.5 g. benzaldehyde and 1.2 g. benzamide (1:2 mol.) were heated together in a 50 c.c. round-bottomed flask on a water-bath for six hours. The mixture first melted to a colourless liquid, which gradually passed on to a straw-yellow and a distinct yellow colour. Water vapours were seen coming out, there being no condenser. After two hours the colour was yellowish brown which became brown after four hours. After six hours' heating, the flask was left overnight. Next morning a dirty brown crystalline solid appeared, which was insoluble in water and in ether. The substance was taken out, crushed and shaken with 20 c.c. of hot water. The insoluble matter was removed by rapid filtration and washed again with hot water to remove all the remaining benzamide. It was washed with small quantities of ether to remove the unreacted aldehyde. The milky white needle-crystals were dried, and melted at 198°. The product was insoluble also in chloroform and benzene, sparingly soluble in methyl alcohol and acetone, and readily soluble in hot alcohol. It was recrystallised thrice from hot dilute alcohol, when the melting point remained stationary at 217.5° (Victor Meyer obtained 218° after recrystallising it four times6). The yield was 0.36 g. or 21.8% of theory.

ii. In the Presence of Pyridine-Trace.—The same amounts were taken with 0.05 c.c. of pyridine (1:2:0.1 mol.) and heated on water-bath for six hours as before. The observations and the procedure were the same. The purified product as well as the mixture of the products of the two experiments gave the same melting point. The yield was 0.39 g. or 23% of theory.

iii. Another experiment with 0.5 mol. of pyridine, i.e., 0.25 c.c., but treated exactly as above, gave the same yield of 23%.

iv. With 0.1 mol. of pyridine, but on reducing the heating to only two hours on water-bath, the yield decreased to 0.2 g. or 12.4% of theory.
v. Taking again no pyridine but heating at 115° for six hours gave a hard dark brown product, which gave, on purification, a good melting point, weighed 1·05 g. and was thus 63·6% in yield. This was the best yield obtained.

vi. When the molecular proportions were 1:1 and there was no pyridine, and the heating was carried out by the smallest flame with asbestos for two hours, the yield was only 8%.

(Found: N = 8·73%; benzyldiene-bisbenzamide C_{11}H_{18}O_{3}N_{2} requires 8·48%. The mono-amide would require 6·69%). It gave no colour with concentrated sulphuric acid and did not decolorise Baeyer's reagent in the cold indicating an absence of unsaturation.

Condensation with Acetamide.

i. In the Absence of any Condensing Agent.—1·0 g. benzaldehyde and 1·2 g. acetamide (1:2) were heated as above on water-bath for six hours. A solid began to separate after 3 hours. Next day a yellow crystalline solid appeared in the cold flask. It was taken out and treated with water and ether as before. Silky white needle-crystals melting at 212° were obtained, which on recrystallisation (hot alcohol) finally melted at 245°. The yield was 0·35 g. or 17·5% of theory, calculated as bisamide. It has been prepared by Roth, and recently by Noyes and Forman, who refluxed the amide and the aldehyde with acetic acid for four hours and who report the melting-point as 238° and a 48% yield.

ii. In the Presence of Pyridine-Trace.—To the same quantities of the aldehyde and the amide, 0.1 c.c. of pyridine was added (1:2:0·1 mol.), and the whole heated as before on a water-bath for six hours. The product melted at 245° and the yield was 0·39 g. or 19·5%.

iii. Heating Without any Condensing Agent for 18 Hours.—The product was hard, brown and in an increased amount. Yield = 1·1 g. or 55% of theory.

iv. Heating at Higher Temperatures.—The heating was at 115° for six hours. The yield was 1·0 g. or 50% of theory. (Found: N = 13·84%; benzyldiene-bisacetamide C_{11}H_{14}O_{2}N_{2} requires 13·59%). Its solubility and reactions were the same as those described for the bis-benzamide derivative.

Condensation with Formamide.

This has been studied by Bülow, whose experiment was repeated.

i. In the Absence of any Condensing Agent.—1·0 g. of benzaldehyde and 0·9 g. of formamide were taken (1:2 mol.) and heated on a water-bath for 24 hours (in four days). Water vapour came out and the colour changed to pale yellow and then to orange-yellow. A sticky solid also made its
appearance, which after treatment with water and ether melted at 130°. On recrystallisation from hot alcohol it became a white crystalline material melting at 148° (Bülow gives 149-50°). It was soluble in hot water and hot alcohol. The yield was only 0·15 g. or 9% of theory.

ii. In the Presence of Pyridine-Trace.—0·1 c.c. of pyridine was added to the same amounts and the mixture was heated on as before. The yield was slightly better, 13·2% of theory.

The product was soluble in hot water and hot alcohol, and gave no reaction with Baeyer’s Reagent and with concentrated sulphuric acid, and was identical with Bülow’s benzylidene-bisformamide.

iii. At Higher Temperature.—Following Bülow, the two were kept in a flask provided with a reflux condenser and heated with a small flame on asbestos wire-gauze, so that it kept on boiling very gently. In five minutes the liquid became pale yellow, yellow and lastly dark brown. The heating was stopped after two hours. The dirty yellow amorphous product, obtained after treatment with water and ether, melted at 240°, and after recrystallisation (alcohol), at 246°, corresponding to Bülow’s 246-47°. It was tetraphenylpyrazine: the yield was only 18% of theory. It decolorised bromine water and alkaline permanganate in the cold and gave a brownish colour with concentrated sulphuric acid.

Condensation with Propionamide.

0·5 G. benzaldehyde and 0·7 g. propionamide were heated alone on a water-bath for three hours. Next morning a pale yellow solid appeared which did not melt on the water-bath. The flask was therefore put on an oil-bath and the bath gradually raised to 120° when the reactants again fused to a yellow liquid. The heating was continued for five hours more, when the product had a brown-yellow colour. The crystalline solid was treated with water and ether and became beautiful milk-white needle crystals, melting at 218°. Recrystallised (alcohol), the melting point rose very little, becoming 220°. (Found: N = 12·56% ; the benzylidene-bispropionamide C₁₃H₁₈N₂ requires 11·97%). The yield was 0·35 g. or 30·7% of theory. Its properties were similar to those of the other bisamides mentioned above.

Condensation with n-Butyramide.

0·5 G. benzaldehyde and 0·9 g. n-butyramide were heated on a water-bath. As only some of the amide dissolved by this time and as higher temperatures are favourable to better yields, the flask was transferred to an oil-bath at 110-15°, when complete fusion to a clear liquid took place. After
Condensation of Aldehydes with Amides—XII

five hours the heating was stopped. Next morning plenty of aldehyde was found still left and so the temperature was raised to 115°. As all the substance did not fuse, the temperature was raised to 130° when a full melting occurred. The heating was carried on for three hours more. The brown solid product was extracted in the usual way. White needle-like crystals melting at 160° were obtained. Recrystallisation (alcohol) raised the melting point to 170°. It had the same properties as described above. (Found: N = 10.74%; benzylidene-bis-n-butyramid C_{18}H_{22}O_{2}N_{2} requires 10.68%). The yield was 1.1 g. or 86% of theory.

Condensation with n-Heptamide.

0.5 G. benzaldehyde and 1.3 g. n-heptamide (1:2 mol.) were heated as usual on water-bath for 5 hours. Next morning a yellow solid mass was seen which smelt distinctly of benzaldehyde and therefore the heating was continued, first on water-bath, later on an oil-bath at 120° when the reactants changed into a yellow liquid. After 2 hours' heating, the bath was raised to 130° and the heating continued for another four hours. The dirty brown mass was treated next morning with water and ether and gave a white crystalline product melting at 124°. Recrystallisation (alcohol) raised the melting point to 128°. (Found: N = 7.92%; benzylidene-bis-n-heptamide C_{21}H_{24}O_{2}N_{2} requires 8.09%). The yield was 0.82 g. or 48.2% of theory. Its reactions were similar to those of the other bisamides above.

Condensation with Cinnamamide.

0.5 G. benzaldehyde and 1.47 g. cinnamamide (prepared in the laboratory from the acid) were heated on an oil-bath at 130°. After four hours in this way, the temperature was raised next day to 160° and the heating continued for 5 hours. Next morning the mass was found to be so hard that it could not be powdered with a glass rod. The usual treatment released a brownish powder melting at 216°. On recrystallisation the melting point rose to 238° and retained a buff colour. (Found: N = 7.26%; benzylidene-biscinnamamide requires 7.33%). The yield was 1.5 g. or 80% of theory. It decolorised bromine water and Baeyer's reagent in the cold, on account of the unsaturation present in cinnamamide.

Condensation of o-Chlorobenzaldehyde

Condensation with Acetamide.

1.4 G. o-chlorobenzaldehyde and 1.2 g. acetamide were taken.

i. In the Absence of any Condensing Agent.—The two were heated on water-bath for 5 hours. A yellow and not a very hard crystalline mass
appeared in the flask next morning, melting at 240°. Recrystallisation (hot alcohol) raised the melting point to 250°. The yield was 0.95 g. or as bisamide 40% of theory.

ii. In the Presence of Pyridine-Trace.—0.1 c.c. of pyridine was added (1:2:0.1 mol.) to the same amount of the two, and the whole was heated for five hours on water-bath. The yellow crystalline product was next day treated as usual, when it gave white needles, melting at 240°, and, after purification at 250°. The yield was 1.05 g. or, as bisamide, 43.4% of theory.

iii. Higher Temperature Without a Condensing Agent.—The aldehyde and the amide were heated alone on an oil-bath at 110° for 5 hours. Next morning the brown product was treated as usual and was changed into white crystals melting at 241°, which on recrystallisation melted at 250°. The yield was 1.3 g. or 54.5% as bisamide. On fusion with sodium, the product showed that it contained chlorine. (Found: Cl = 14.33%; o-chlorobenzylidenebisacetamide \( \text{C}_{13}\text{H}_{13}\text{O}_{2}\text{N}_2\text{Cl} \) requires 14.76%. The mono-amide would require 19.55%. (Found: N = 11.48%; the above bisacetamide requires 11.22%).) Its properties were similar to those of the corresponding benzylidene-bisacetamide.

Condensation with Propionamide.

o-Chlorobenzaldehyde 1·4 g. and propionamide 1·5 g. were taken.

i. In the Absence of any Condensing Reagent.—The two were heated alone on water-bath for 5 hours. Next day they had to be kept on an oil-bath at 115° to ensure fusion, the heating being for 5 hours. Brown hard crystalline mass soon changed to white crystals under the usual treatment, and melted at 210°, the recrystallised pure product melting at 216°. The yield was 1.8 g. or as bispropionamide 67% of theory.

ii. In the Presence of Pyridine-Trace.—The same amounts were heated with 0·1 c.c. of pyridine (1:2:0.1 mol.) on water-bath for 4 hours and, the next day, on an oil-bath at 115° for 5 hours. The product came out as usual, weighing 1.9 g. or as bisamide 68.3% of theory. The melting and the mixed melting points were identical, and so were its properties. (Found: Cl = 12.99%; o-chlorobenzylidenebispropionamide \( \text{C}_{13}\text{H}_{13}\text{O}_{2}\text{N}_2\text{Cl} \) requires 13.22%)

Condensation with n-Butyramide.

o-Chlorobenzaldehyde 1·4 g. and n-butyramide 1·75 g. (1:2 mol.) were taken.

i. Heating alone at 130°.—The two were heated on a water-bath for 4 hours on one day and the next day at 120° for another 2 hours and at
125-30° for 2 hours more. After purification the product melted at 173° and after recrystallisation the final melting point was 180°. The yield was 1.9 g. or 64.2% of theory.

ii. Heating alone up to 145°.—The heating was for 3 hours at 130° and for 3 hours at 140-45°. The product was 2.5 g. or 86% of theory. (Found: Cl = 11.64%; the o-chlorobenzylidene-bis-n-butyramide \( \text{C}_{12}\text{H}_{19}\text{O}_{2}\text{N}_{2}\text{Cl} \) requires 11.97%.)

Condensation with Benzamide.

i. In the Absence of any Condensing Agent.—o-Chlorobenzaldehyde 1.4 g. and benzamide 2.4 g. were heated together first on water-bath and then on an oil-bath at 110° for about 4 hours in all. The next day the mixture was heated at 140° for 3 hours. The crude white crystals melted at 200°; recrystallised (dilute hot alcohol) the product melted at 215°. The yield was 2.5 g. or 70% of theory.

ii. In the Presence of Pyridine-Trace.—In the presence of 0.1 mol. of pyridine and heated at 110° for three hours and 140° for another three hours, the same product was obtained, melting at 215° after recrystallisations. The yield was 2.7 g. or 74.5% of theory. (Found: Cl = 9.39%; o-chlorobenzylidene-bisbenzamide \( \text{C}_{24}\text{H}_{14}\text{O}_{2}\text{N}_{2}\text{Cl} \) requires 9.74%.)

Condensation with Formamide.

In the Absence of any Condensing Agent.—o-Chlorobenzaldehyde 1.4 g. and formamide 0.9 g. were heated alone. In one experiment, (i) on water-bath for 30 hours in 5 days. A brown sticky mass was obtained, which, by means of the usual process, gave a crude product melting at 169°. When recrystallised (alcohol), it finally melted at 176°. It was straw yellow in colour. The yield was only 8% of the theory, as bisamide. In the second experiment, (ii) the two were heated at 140° for five hours. Next morning a dark brown viscous liquid was left. It was washed with water. On treating it with ether, it was found to dissolve completely in it, leaving no insoluble solid. After the evaporation of ether, it was shaken up with a saturated solution of sodium bisulphite, when some solid derivative, possibly of the aldehyde, separated. But the residue remained a liquid from which no solid derivative could be isolated. It was obvious that the heating was insufficient.

The solid obtained in (i) gave on analysis Cl = 16.3%; o-chlorobenzylidenebisformamide \( \text{C}_{9}\text{H}_{10}\text{O}_{2}\text{N}_{2}\text{Cl} \) requires 16.70%. Its properties were similar.
Condensation with \(n\)-Heptamide.

\(o\)-Chlorobenzaldehyde 1.4 g. and \(n\)-heptamide 2.6 g. (1:2 mol.) were heated on a water-bath for two hours, when a solid began to separate. The heating was continued at 110° for four hours; more solid separated in the beginning but later on it went into solution, thus at the end of the heating there was no solid in the flask. Next morning the solid that had come out was found to contain plenty of the free aldehyde, and so the heating was continued at 125° when the solid again went in solution. After 2 hours a solid again came out which increased in amount gradually, the heating being stopped after five hours. The hard brown crystalline product found next morning, gave after the usual treatment, a white crystalline product melting at 135°, and after recrystallisation, 141°. (Found: Cl = 9.09%; \(o\)-chlorobenzylidene-\(n\)-heptamide \(C_{25}H_{32}O_2N_2Cl\) requires 9.32%). The yield was 3.1 g. or 81.6% of theory. Its properties were similar.

Condensation with Cinnamamide.

\(o\)-Chlorobenzaldehyde 1.4 g. and cinnamamide 2.9 g. were heated together (1:2 mol.) first on water-bath and then on an oil-bath at 120° when the reactants melted to a brown liquid. After 2 hours the temperature had to be raised to 130° for 2 hours and to 140° for another 2 hours. The next day the hard dark brown mass, on the usual treatment, gave a brown powder melting at 216° which, after several recrystallisations, melted finally at 232°. It was a buff coloured substance. (Found: Cl = 8.08%; \(o\)-chlorobenzylidene-bis-\(n\)-heptamide \(C_{25}H_{32}O_2N_2Cl\) requires 8.52%). The yield was 3 g. or 72% of theory. As before in the case of the benzaldehyde compound, it decolorised bromine water and Baeyer’s reagent in the cold and gave a brown colour to concentrated sulphuric acid.

<table>
<thead>
<tr>
<th>Amides</th>
<th>Maximum yield</th>
<th>Melting point</th>
<th>Maximum yield</th>
<th>Melting point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formamide</td>
<td>13.2</td>
<td>148° C.</td>
<td>8</td>
<td>176° C.</td>
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<tr>
<td>Acetamide</td>
<td>55</td>
<td>245° C.</td>
<td>54-5</td>
<td>250° C.</td>
</tr>
<tr>
<td>Propionamide</td>
<td>30-7</td>
<td>220° C.</td>
<td>68</td>
<td>210° C.</td>
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<td>(n)-Butyramide</td>
<td>86</td>
<td>170° C.</td>
<td>86</td>
<td>180° C.</td>
</tr>
<tr>
<td>(n)-Heptamide</td>
<td>48-2</td>
<td>128° C.</td>
<td>81-6</td>
<td>141° C.</td>
</tr>
<tr>
<td>Benzamide</td>
<td>63-8</td>
<td>217-5° C.</td>
<td>74-5</td>
<td>215° C.</td>
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<tr>
<td>Cinnamamide</td>
<td>80</td>
<td>238° C.</td>
<td>72</td>
<td>240° C.</td>
</tr>
</tbody>
</table>

Benzaldehyde

\(o\)-Chloro-benzaldehyde

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SUMMARY

The condensation of benzaldehyde and of o-chlorobenzaldehyde with several amides has been studied, in the presence as well as in the absence of pyridine. The base slightly increased the yield in many cases. The rise of temperature as well as the prolongation of heating raised the yield more effectively. All the products were the corresponding bisamides. The presence of chlorine on the aromatic ring of the aldehyde, had the expected tendency to increase the yield, particularly in the condensations with benzamide, propionamide and n-heptamide. Condensations with formamide, as has been the general experience, did not give good yields; in all other cases, the yields were good, starting from 30% and reaching up to 86% in some cases.

REFERENCES

2. Pandya and Sodhi. .. Ibid., 1938, 7, 361.
4. Roth. .. Annal., 1870, 154, 72-76.