

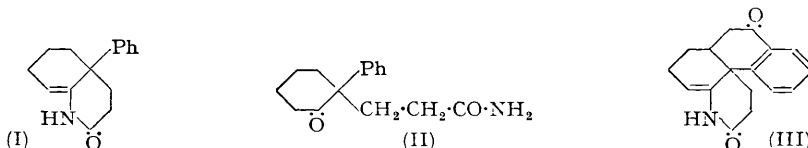
843. Acrylamide as an Acceptor in the Michael Condensation.

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The Michael condensation of acrylamide with a number of ketones has been carried out in yields ranging from 20% to 70%.

THE cyanoethylation reaction has been useful in the production of many synthetic intermediates (Bruson, "Organic Reactions," Vol. 5, p. 79, Wiley, New York, 1949), but when a product containing a 2-carbamoylethyl group is desired, it is often difficult to effect partial hydrolysis of the β -cyano-group. Particularly since intermediates containing the 2-carbamoylethyl group were of interest in connection with synthetic morphine studies (cf. Ginsburg and Pappo, *J.*, 1953, 1524), the possibility of effecting the carbamoylethylation reaction has been studied.

Only one case of Michael condensation in which acrylamide acts as the acceptor has been reported, that with 2-nitropropane as donor (Bruson, U.S. P. 2,370,142; *Chem. Abs.*, 1945, 39, 3544). The Michael condensation of a number of ketones with acrylamide has now been carried out. It was possible to isolate the products of carbamoylethylation in most cases. With acetophenone, however, a heavy oil was obtained; that reaction had occurred was shown by hydrolysis of the adduct to the corresponding substituted butyric acid. In most cases, the 2-carbamoylethyl derivative, which is undoubtedly the primary product, lost a mole of water to yield the corresponding lactam. For example, in the carbamoylethylation of 2-phenylcyclohexanone the resulting amide did not show absorption in the infra-red at about 5.84μ . The alicyclic carbonyl group disappeared owing to the formation of the lactam (I) rather than the 2-carbamoylethyl derivative (II). Elementary analysis agreed with the infra-red assignment. Hydrolysis of the lactam yielded 2-oxo-1-phenylcyclohexylpropionic acid identical with that prepared by hydrolysis of 2-oxo-1-phenylcyclohexylpropionitrile.



Similarly, carbamoylethylation of 1:2:3:4:9:10:11:12-octahydro-4:9-dioxo-phenanthrene did not yield the previously reported 12-2'-carbamoylethyl derivative, m. p. 205° (Ginsburg and Pappo, *loc. cit.*), but a product, m. p. $286-289^\circ$, for which the analytical figures correspond to the lactam (III). In the latter compound the strong band at 5.84μ which is present in the amide, m. p. 205° , was absent. Both the primary amide and the lactam on hydrolysis yielded the same acid, 12-2'-carboxyethyl-1:2:3:4:9:10:11:12-octahydro-4:9-dioxo-phenanthrene.

Carbamoylethylation of cyclohexanone gave the lactam formed by monosubstitution, albeit in low yield, when sodium hydride-sodium methoxide was used to effect the condensation at room temperature. Heating increased the formation of more highly substituted derivatives.

Acetophenone yielded an oily adduct which on hydrolysis gave γ -benzoylbutyric acid, identical with the product obtained by treatment of 2-phenylcyclopentanone with *n*-amyl nitrite and sodium ethoxide and subsequent hydrolysis of the resulting oxime (cf. Elad and Ginsburg, *J.*, 1953, 2664).

Dibenzyl ketone yielded the symmetrical diamide as shown by the failure to obtain a condensation product of the corresponding diacid with furfuraldehyde.

EXPERIMENTAL

Michael Condensation.—(a) *With potassium tert.-butoxide.* To dry potassium *tert.*-butoxide [prepared by dissolving potassium (0.4 g., 0.01 mole) in *tert.*-butanol (15 ml.) and removal of excess of solvent *in vacuo*] was added the ketone (0.01 mole) in dry dioxan (15–20 ml.), and the

mixture was heated under reflux for 2.5–3 hr. A solution of acrylamide (0.71 g., 0.01 mole) in dry dioxan (15 ml.) was added in one portion to the boiling mixture, and heating was continued for a further 2.5–3 hr. The solvent was removed *in vacuo* and benzene (50 ml.) and hydrochloric acid (1 : 1; 20 ml.) were added to the residue. The acid layer was extracted once with benzene, and the combined benzene extracts were dried (Na_2SO_4) and concentrated to 5–10 ml. Subsequent treatment varied in each case (see below).

(b) *With sodamide.* Sodamide (0.01 mole), the corresponding ketone (0.01 mole), dry benzene (10 ml.), and dry ether (5 ml.) were heated under reflux for 3 hr. A solution of acrylamide (0.01 mole) in dioxan (20 ml.) was added in one portion and heating was continued for 3 hr. Subsequent treatment was similar to that in procedure (a).

Hydrolysis of Amide to Acid.—A mixture of amide or lactam (1 g.), acetic acid (15 ml.), concentrated hydrochloric acid (5 ml.), and water (5 ml.) was boiled for 12 hr. (cf. Bachmann and Fornefeld, *J. Amer. Chem. Soc.*, 1951, **73**, 51). The mixture was poured into a large volume of water and then extracted with ether, and the ether extract was shaken with dilute sodium hydroxide solution. After acidification, the acid was either obtained as a solid or, if as an oil, it was re-extracted with ether and crystallised from the appropriate solvent after evaporation of the ether.

Carbamoylethylation of 2-Phenylcyclohexanone.—Ether was added to the concentrated benzene solution of the product. The lactam (I) formed clusters of prisms, m. p. 208–210° (from benzene–ether); the yields were 29% (procedure b) and 39% (procedure a) (Found : C, 79.2; H, 7.3. $\text{C}_{15}\text{H}_{17}\text{ON}$ requires C, 79.2; H, 7.5%).

After evaporation of the solvent the residual oil in the mother-liquor was hydrolysed according to the general procedure. The crude acid obtained was recrystallised from heptane; it had m. p. 113–115°; the yields were 22% (procedure b) and 29% (procedure a). It gave no m. p. depression on admixture with authentic 2-oxo-1-phenylcyclohexylpropionic acid obtained by hydrolysis of the corresponding nitrile. Bachmann and Fornefeld (*loc. cit.*) report m. p. 114–114.5° for this acid.

Carbamoylethylation of 1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-Octahydro-4-oxophenanthrene.—Ether was added to the concentrated benzene solution and the solution set aside overnight. The lactam formed prismatic needles (23%, procedure a), m. p. 234–236° (from dilute acetic acid) (Found : C, 80.4; H, 7.9. $\text{C}_{17}\text{H}_{19}\text{ON}$ requires C, 80.6; H, 7.6%).

Hydrolysis of the lactam yielded the corresponding acid, m. p. and mixed m. p. 110° (Ginsburg and Pappo, *loc. cit.*). The crude oil remaining in the mother-liquor was also hydrolysed and yielded the same acid in 27% yield.

Carbamoylethylation of 1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-Octahydro-4 : 9-dioxophenanthrene.—A modification of procedure (b) was used in which sodamide was replaced by sodium hydride; a small amount of methanol was added to start the reaction. Addition of ether to the benzene solution yielded platelets of the lactam (III) (25%), m. p. 286–289° (from dilute acetic acid). Procedure (a) gave the same product in 23% yield (Found : C, 76.3; H, 6.2. $\text{C}_{17}\text{H}_{17}\text{O}_2\text{N}$ requires C, 76.4; H, 6.4%).

Seeding of the mother-liquor with authentic 12-2'-carbamoylethyl derivative, m. p. 205° (Ginsburg and Pappo, *loc. cit.*), did not induce crystallisation of any uncyclised amide. Hydrolysis of the oil in the mother-liquor afforded the corresponding acid, m. p. 153° (Ginsburg and Pappo, *loc. cit.*), in 16% yield. Hydrolysis of the lactam yielded the same acid, identical with that formed by hydrolysis of the primary amide.

Carbamoylethylation of cycloHexanone.—Sodium hydride was used as catalyst. Addition of acrylamide and subsequent treatment was carried out at room temperature. The product crystallised from the concentrated benzene solution. After two recrystallisations leaflets, m. p. 142–143° (from heptane–benzene), were obtained in 10% yield. The same product was formed in 10% yield by procedure (b) (Found : C, 71.5; H, 8.8. Calc. for $\text{C}_9\text{H}_{13}\text{ON}$: C, 71.5; H, 8.7%).

Lions (*J. Proc. Roy. Soc., N.S. Wales.*, 1938, **71**, 192; *Chem. Abs.*, 1938, **32**, 5843) reports m. p. 142° for 1 : 2 : 3 : 4 : 5 : 6 : 7 : 8-octahydro-2-oxoquinoline.

Hydrolysis of the lactam gave β -2-oxocyclohexylpropionic acid, m. p. 63–64° (from hexane). Hydrolysis of the residual oil in the mother-liquor afforded an additional 16% yield of the acid, m. p. 63–64°. The semicarbazone melted at 183–184° (from methanol). Mannich and Koch (*Ber.*, 1942, **75**, 803) report m. p. 65° and 186° for the acid and its semicarbazone, respectively.

Carbamoylethylation of 2-Phenylcycloheptanone.—The lactam crystallised from the concentrated benzene solution; it had m. p. 227–228° (from benzene); the yields were 31% (procedure a) and 10% (procedure b) (Found : C, 79.6; H, 8.2. $\text{C}_{16}\text{H}_{19}\text{ON}$ requires C, 79.6; H, 7.9%).

Hydrolysis of the oil in the mother-liquor gave β -2-oxo-1-phenylcycloheptylpropionic acid,

m. p. 105—106° (from hexane), in 12% yield. Hydrolysis of the lactam gave the same acid (Found : C, 73.8; H, 7.4. $C_{16}H_{20}O_3$ requires C, 73.8; H, 7.7%).

Carbamoylethylation of Acetophenone.—The product could not be crystallised, but hydrolysis of the heavy oil afforded γ -benzoylbutyric acid (20%, procedure *a*), m. p. 124—126° (from heptane) (Found : C, 69.0; H, 6.5. Calc. for $C_{11}H_{12}O_3$: C, 68.7; H, 6.3%).

Fuson and his co-workers (*J. Amer. Chem. Soc.*, 1934, **56**, 235) report m. p. 126° for this acid. The product was identical with that obtained by the following procedure (Elad and Ginsburg, *loc. cit.*).

γ -Benzoylbutyric acid. To a solution of sodium ethoxide [from sodium (0.23 g.) and absolute ethanol (5 ml.)] was added a solution of 2-phenylcyclopentanone (1.6 g.) in ethanol (5 ml.). *n*-Amyl nitrite (1.7 ml.) was added in one portion with ice-cooling. The mixture was kept in the refrigerator for 48 hr. with occasional shaking. After acidification with acetic acid and dilution with water the mixture was extracted with ether. The ether solution was extracted with Claisen solution; the alkaline layer was acidified with hydrochloric acid to pH = 1 and refluxed for 3 hr. After extraction with ether and re-extraction of the ether solution with aqueous sodium hydroxide, the alkaline solution was acidified. γ -Benzoylbutyric acid, m. p. 124—126° (from heptane), was precipitated.

Carbamoylethylation of Dibenzyl Ketone.—Addition of heptane to the concentrated benzene solution caused a heavy oil to separate. This partly crystallised during 2 days. Filtration gave the *diamide* (20%, procedure *a*) as thick rhombs, m. p. 168—169° (from benzene) (Found : N, 7.6. $C_{21}H_{24}O_3N_2$ requires N, 7.95%).

Hydrolysis of the diamide gave the *diacid* which can be obtained in two interconvertible forms : α , m. p. 141—143° (from benzene-heptane); β , m. p. 123—125° (from heptane) (Found : C, 71.0; H, 6.6. $C_{21}H_{22}O_5$ requires C, 71.2; H, 6.3%). No condensation product could be obtained with furfuraldehyde. Hydrolysis of the oil afforded 28% additional yield of the diacid (based on dibenzyl ketone).

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