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546.264.267.04

The Chemistry of Carbonyl Cyanide. Dienophilic Properties of Carbonyl Cyanide and Diethyl Mesoxalate. Formation of Dihydropyran Derivatives

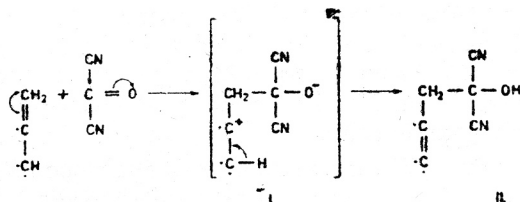
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Received June 13, 1957

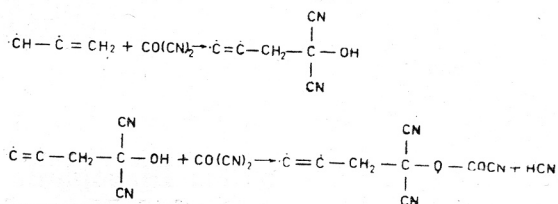
The reactions of carbonyl cyanide with butadiene or 2,3-dimethylbutadiene have been studied. In either case there was found to take place diene condensation leading to corresponding derivatives of dihydropyran. Dihydropyran derivatives synthesis was also found to occur when diethyl mesoxalate was condensed with the dienes. The correctness of the structure of the adducts obtained was established by degradation experiments.

Recent work* on the chemistry of carbonyl cyanide carried out in our Laboratory revealed among others a significant fact: when the previously studied¹ reactions of this unique cyanide with certain olefins containing the $\cdot\text{CH}-\text{C}=\text{C}\cdot$ grouping (e. g. alpha-methylstyrene, trimethylethylene) are conducted at low temperatures under strictly controlled conditions, they proceed without evolution of hydrogen cyanide, an unsaturated hydroxy addition product of the general formula II being formed in almost theoretical yield. This result, evidently in agreement with the earlier advanced hyperconjugation concept¹, permits of a deeper insight into the nature of the reaction, disclosing a striking analogy to the so called en-syntheses, and a mechanism is now proposed which involves as a first step an electrophilic attack by carbonyl cyanide on the grouping $\cdot\text{CH}-\text{C}=\text{C}\cdot$ in the olefin. This would give the transient intermediate I which becomes stabilized by an intramolecular proton transfer from carbon in the allylic position to oxygen to form the addition product II:



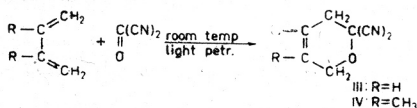
Another consequence of isolating products of structure II is that it proves our earlier scheme of the reaction between olefins and two mols of carbonyl cyanide to be inaccurate, the correct representation being:

* carried out by Mrs. F. Werner-Zamojska and to be shortly published elsewhere.



The formation of hydroxylic products II considered in association with the mild conditions and the high yield of the reaction suggests that the mode of addition of olefins to carbonyl cyanide implies, and primarily depends on, an unusually high polarisation of the C=O bond in carbonyl cyanide.

This view is now strongly supported by the results of our investigations on the reaction between carbonyl cyanide and butadiene or 2,3-dimethylbutadiene, viz., in either case a diene condensation was found to take place, with the formation of a corresponding dihydropyran derivative: 6,6-dicyano-5,6-dihydro-1,2-pyran (III, m. p. 16°, b. p. 69—70°/2 mm) or 3,4-dimethyl-6,6-dicyano-5,6-dihydro-1,2-pyran (IV, m. p. 24—26°, b. p. 62°/0.8 mm):



The condensations again proceeded at room temperature, at a rapid pace (15 min. in the case of dimethylbutadiene) and with a high yield. This is worthy of note since in most cases hitherto described² diene condensations starting with carbonyl compounds and leading to dihydropyran derivatives require drastic conditions (150—185°, 6—24 hours) while giving poor yields (10—50%).

The structure of the adducts III and IV, which have not yet been described in literature, was established by routine degradation methods. And here is a brief account of the results obtained.

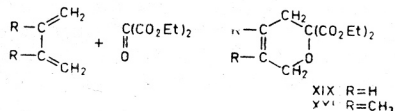
The adduct III yielded upon alkaline hydrolysis two mols of ammonia and a dicarboxylic acid (5,6-dihydro-1,2-pyran-6,6-dicarboxylic, V; di-*p*-bromophenacyl ester, VI, m. p. 166—167°; diamide, VII, m. p. 228—230°) which readily decarboxylated affording a monocarboxylic acid (5,6-dihydro-1,2-pyran-6-carboxylic, VIII, b. p. 60°/0.005 mm; *p*-bromophenacyl ester, IX, m. p. 127—128°). Hydrogenolysis of the latter furnished a dihydroacid (tetrahydro-pyran-2-carboxylic, X, b. p. 100°/2.3 mm.) the *p*-bromophenacyl ester of which XI, m. p. 101—102° proved to be identical with that prepared from synthetic tetrahydro-pyran-2-carboxylic acid³.

Degradation of adduct IV was run on exactly the same lines and analogous products were obtained. These were in order: a dicarboxylic acid (3,4-dimethyl-5,6-dihydro-1,2-pyran-6,6-dicarboxylic, XII, m. p. 136—137°; dimethyl ester, XIII, b. p. 160°/16 mm.; diamide, XIV, m. p. 268—269°), a monocarboxylic acid (3,4-dimethyl-5,6-dihydro-1,2-pyran-6-carboxylic, XV, m. p. 85—86°; amide, XVI, m. p. 164°) and a dihydroderivative of the latter (4,5-dimethyl-tetrahydro-pyran-2-carboxylic acid, XVII, b. p. 137—138°/10 mm.; *p*-bromo-phenacyl ester,

XVIII, m. p. 126—127°). Diamide XIV was found to be identical with that prepared from the condensation product of diethyl mesoxalate and 2,3-dimethylbutadiene (see below).

It is evident that the recognition of the dienophilic properties of carbonyl cyanide opens new possibilities for the synthesis of pyran derivatives, although the present technical difficulties in obtaining the reagent detract somewhat its usefulness in practice.

On the other hand, the recognition of the dienophilic reactivity of carbonyl cyanide strongly suggested existence of such properties in other carbonyl compounds having, like carbonyl cyanide, two strongly negative substituents attached to the carbonyl group. Preliminary experiments appear to confirm this surmise at least with regard to some of the compounds. For instance, diethyl mesoxalate would condense with butadiene or 2,3-dimethylbutadiene to yield diethyl 5,6-dihydro-1,2-pyran-6,6-dicarboxylate (XIX, b. p. 142—144°/20 mm.; diamide, XX, m. p. 228—230° identical with VII) and diethyl 3,4-dimethyl-5,6-dihydro-1,2-pyran-6,6-dicarboxylate (XXI, b. p. 107—108°/0.5 mm.; diamide, XXII, m. p. 269—270° identical with XIV) respectively:



As expected, unlike in the case of carbonyl cyanide, the condensations called for drastic conditions (4 hours at 70—110° for dimethylbutadiene, 6 hours at 135° for butadiene, the yields being 52% and 37% respectively).

EXPERIMENTAL

Melting points are uncorrected. Experiments with carbonyl cyanide were carried out in vessels carefully protected against moisture. Light petroleum refers to the fraction of boiling range 40—60°.

A. Condensation of Carbonyl Cyanide with Butadiene

6,6-Dicyano-5,6-dihydro-1,2-pyran (III)

Carbonyl cyanide (12 g.) and butadiene (12 g.) were mixed in light petroleum (75 ml.) at room temperature. A yellowish green colour appeared and gradually faded. After 18 hours the addition product separated as a slightly yellow oil; the colour disappeared upon distillation under reduced pressure, b. p. 69—70°/2 mm., (15.3 g., 75%), d_4^{20} 1.110, n_D^{20} 1.4621. When the purified oil was refrigerated (CO₂ + acetone) it solidified to a hard crystalline mass, m. p. 16°, readily soluble in simple organic solvents, except light petroleum.

Anal. 26.00 mg. subst.: 59.59 mg. CO₂, 10.0 mg. H₂O
 14.02 mg. subst.: 2.592 ml. N₂ (21.5°, 747.3 mm.)
 C₇H₆ON₂ (134.1) calc'd: C 62.68; H 4.51; N 20.89%
 found: C 62.61, H 4.45; N 21.03%

5,6-Dihydro-1,2-pyran-6,6-dicarboxylic acid (V)

The dicyano compound III (23.7 g.) was refluxed with 10% aqueous sodium hydroxide (200 ml.) until ammonia evolution ceased (15 hours). The clear solution was cooled, acidified with excess of 20% hydrochloric acid and extracted with ether. After evaporation of the extract under reduced pressure, the dicarboxylic acid V

remained as a pale straw-coloured oil (26 g., 85%). Since it decomposed on distillation (decarboxylation, vide below) and failed to crystallize, it could not be obtained in analytically pure state. The composition of the acid was established by analysis of its Ag-salt, di-*p*-bromo-phenacyl ester and diamide.

Anal. 3.282 mg. subst.: 2.563 mg. CO₂, 0.563 mg. H₂O
1.828 mg. Ag
C₇H₆O₅Ag₂ (385.9) calc'd: C 21.78; H 1.57; Ag 55.90%
found: C 21.31; H 1.54; Ag 55.73%

Di-*p*-bromo-phenacyl 5,6-dihydro-1,2-pyran-6,6-dicarboxylate (VI) prepared in the usual way formed minute colourless needles, m. p. 166–167° (from ethanol).

Anal. 31.86 mg. subst.: 57.12 mg. CO₂, 8.84 mg. H₂O
C₂₃H₁₆O₇Br₂ (566.2) calc'd: C 48.77; H 3.20%
found: C 48.80; H 3.11%

5,6-Dihydro-1,2-pyran-6,6-dicarboxylic acid diamide (VII)

Dry, freshly precipitated (from the disodium salt by means of silver nitrate) disilver salt of the acid V (4.6 g.) was refluxed for 2 hours with ethyl iodide (7 g.) in benzene solution (20 ml.). The resulting slightly yellow oily diethyl ester (1.35 g.) which showed no tendency to crystallize, was mixed with 25% ammonia (15 ml.), shaken at room temperature for 3 hours and left overnight. The mixture was evaporated to one third of its volume. The diamide separated as a copious crystalline precipitate. Recrystallized from water, the derivative formed thick plates, m. p. 228–230°.

Anal. 30.00 mg. subst.: 54.24 mg. CO₂, 14.83 mg. H₂O
C₇H₁₀O₃N₂ (170.1) calc'd: C 49.40; H 5.92%
found: C 49.34; H 5.53%

5,6-Dihydro-1,2-pyran-6-carboxylic acid (VIII)

The dicarboxylic acid V (9.59 g.) was heated in a metal bath at 120° until carbon dioxide evolution stopped (30 min.). The slightly coloured decarboxylation product was distilled under reduced pressure (4.3 g., 60%). Colourless oily liquid, b. p. 60°/0.005 mm., d_4^{20} 1.218, n_4^{20} 1.4831.

p-Bromo-phenacyl 5,6-dihydro-1,2-pyran-6-carboxylate (IX) formed glistening plates, m. p. 127–128° (from ethanol).

Anal. 21.24 mg. subst.: 40.58 mg. CO₂, 7.81 mg. H₂O
C₁₄H₁₃O₄Br (325.1) calc'd: C 51.69; H 4.03%
found: C 52.14; H 4.12%

Tetrahydro-pyran-2-carboxylic acid (X)

The acid VIII (3.5 g.) in ethanol solution (50 ml.) was agitated with platinum oxide (0.5 g.) in an atmosphere of hydrogen at room temperature. After 3 hours hydrogen uptake was complete and corresponded to 1 mol of hydrogen. Removal of the catalyst and evaporation of the solvent afforded a colourless oil, b. p. 100°/2.3 mm., (3 g., 84%), n_D^{20} 1.4618.

Anal. 18.60 mg. subst.: 37.32 mg. CO₂, 12.80 mg. H₂O
C₆H₁₀O₃ (130.1) calc'd: C 55.37; H 7.75%
found: C 54.76; H 7.70%

p-Bromo-phenacyl tetrahydro-pyran-2-carboxylate (XI) crystallized from ethanol in glistening needles, m. p. 101–102°. On admixture with the *p*-bromo-

phenacyl ester prepared from synthetic tetrahydro-pyran-2-carboxylic acid³, the melting point remained unchanged.

Anal. 21.50 mg. subst.: 40.58 mg. CO₂, 8.43 mg. H₂O
 C₁₄H₁₅O₄Br (327.1) calc'd: C 51.39; H 4.62%
 found: C 51.50; H 4.39%

B. Condensation of Carbonyl Cyanide with 2,3-Dimethylbutadiene

3,4-Dimethyl-6,6-dicyano-5,6-dihydro-1,2-pyran (IV)

Carbonyl cyanide (15.3 g.) was added dropwise with cooling to dimethylbutadiene (15.7 g.) dissolved in light petroleum (20 ml.). An orange colour appeared, turned rapidly yellow and faded after 15 min. Thereupon, the solvent was removed at the water pump and the residue distilled in high vacuo. Colourless oil, b. p. 62°/0.8 mm. (28.48 g., 92%), d_4^{25} 1.047, n_D^{25} 1.4631. Upon refrigeration (CO₂+acetone) it solidified to a hard transparent crystalline glacial mass, m. p. 24—26°, readily soluble in usual organic solvents.

Anal. 2.562 mg. subst.: 6.274 mg. CO₂, 1.338 mg. H₂O
 3.813 mg. subst.: 0.586 ml. N₂ (19°, 731.16 mm.)
 C₉H₁₀ON₂ (162.2) calc'd: C 66.65; H 6.22; N 17.27%
 found: C 66.82; H 5.84; N 17.28%

3,4-Dimethyl-5,6-dihydro-1,2-pyran-6,6-dicarboxylic acid (XII)

The dicyano derivative IV (15.8 g.) and 17% aqueous sodium hydroxide (400 ml.) were refluxed for 15 hours with occasional shaking. The cooled mixture was made acid with excess of dilute sulphuric acid, and the acidic hydrolysis product was isolated by ether extraction. Crystallized from benzene-ethanol (9:1) the product formed transparent well shaped prismatic plates, m. p. 113—114°, readily soluble in water, simple alcohols and ether, sparingly soluble in benzene. On drying at 100° the crystals became opaque and the melting point was raised to 136—137°. In a quantitative experiment 2.24 g. of the specimen, m. p. 113—114°, dried at 100° *in vacuo* lost 0.19 g. or 8.5%, whereas C₉H₁₂O₅·H₂O, losing H₂O, requires a loss of 8.3%. The dried material gave the following analytical figures.

Anal. 2.395 mg. subst.: 4.762 mg. CO₂, 1.316 mg. H₂O
 C₉H₁₂O₅ (200.2) calc'd: C 53.99; H 6.04%
 found: C 54.26; H 6.10%

Dimethyl 3,4-Dimethyl-5,6-dihydro-1,2-pyran-6,6-dicarboxylate (XIII)

The ester was obtained from the dicarboxylic acid XII by the procedure adopted for the preparation of the diethyl ester of V. Colourless oily liquid, b. p. 160°/16 mm., p_4^{20} 1.155, n_D^{20} 1.4720.

Anal. 23.44 mg. subst.: 49.62 mg. CO₂, 14.70 mg. H₂O
 C₁₁H₁₆O₅ (228.2) calc'd: C 57.88; H 7.07%
 found: C 57.77; H 7.02%

3,4-Dimethyl-5,6-dihydro-1,2-pyran-6,6-dicarboxylic acid diamide (XIV) prepared from the dimethyl ester XIII, formed opaque leaflets, m. p. 268—269° (from aqueous solution), undepressed on admixture with the diamide XXII.

Anal. 27.99 mg. subst.: 55.48 mg. CO₂, 17.40 mg. H₂O
 2.377 mg. subst.: 0.304 ml. N₂ (25°, 732.08 mm.)
 C₉H₁₄O₃N₂ (198.2) calc'd: C 54.53; H 7.12; N 14.13%
 found: C 54.58; H 7.07; N 14.12%

3,4-Dimethyl-5,6-dihydro-1,2-pyran-6-carboxylic acid (XV)

The dicarboxylic acid XII (7 g.) was heated in a metal bath at 140—150°. Carbon dioxide evolution stopped after 30 min. The product (4.2 g., 77%) crystallized from

carbon tetrachloride or carbon sulphide in clusters of hard colourless prismatic plates, m. p. 85—86°, readily soluble in water, ethanol and ether.

Anal. 2.380 mg. subst.: 5.353 mg. CO₂, 1.663 mg. H₂O
C₈H₁₂O₃ (156.2) calc'd: C 61.52; H 7.75%
found: C 61.38; H 7.82%

3,4-Dimethyl-5,6-dihydro-1,2-pyran-6-carboxylic amide (XVI) formed glistening elongated tablets, m. p. 164° (from aqueous solution).

Anal. 2.807 mg. subst.: 6.406 mg. CO₂, 2.099 mg. H₂O
2.777 mg. subst.: 0.227 ml. N₂ (20°, 735.32 mm.)
C₈H₁₃O₂N (155.2) calc'd: C 61.91; H 8.44; N 9.03%
found: C 62.28; H 8.37; N 9.21%

4,5-Dimethyl-tetrahydropyran-2-carboxylic acid (XVII)

The catalytic hydrogenation of acid XV (7.21 g.) was carried out in presence of platinum oxide. Hydrogen uptake (1 mol) stopped after 6 hours. After removal of catalyst and solvent by filtration and distillation respectively, the colourless oily hydrogenolysis product was distilled, b. p. 137—138°/10 mm., (6.44 g., 88.2%), d₄²⁰ 1.091, n₄²⁰ 1.4650.

Anal. 1.966 mg. subst.: 4.354 mg. CO₂, 1.513 mg. H₂O
C₈H₁₄O₃ (158.2) calc'd: C 60.74; H 8.92%
found: C 60.44; H 8.61%

p-Bromo-phenacyl 4,5-dimethyl-tetrahydropyran-2-carboxylate (XVIII) prepared in the usual way, crystallized from ethanol in soft, minute colourless needles, m. p. 126—127°.

Anal. 20.29 mg. subst.: 40.20 mg. CO₂, 9.62 mg. H₂O
C₁₆H₁₀O₄Br (355.2) calc'd: C 54.12; H 5.39%
found: C 54.07; H 5.31%

C. Condensation of Diethyl Mesoxalate with Butadiene or 2,3-Dimethylbutadiene

Diethyl 5,6-Dihydro-1,2-pyran-6,6-dicarboxylate (XIX)

A mixture of diethyl mesoxalate (10 g.), butadiene (6 g.) and hydroquinone (0.3 g.) was heated in a sealed tube for 6 hours at 135°. The pale yellow oily adduct isolated by fractionation under reduced pressure from the dark reaction product, boiled 142—144°/20 mm., (4.82 g., 37%).

5,6-Dihydro-1,2-pyran-6,6-dicarboxylic acid diamide (XX) obtained by shaking the diethyl ester XIX with 25% ammonia, crystallized from aqueous solution in thick plates, m. p. 228—230°. The melting point was undepressed upon admixture with the diamide VII.

Anal. 19.46 mg. subst.: 35.26 mg. CO₂, 9.67 mg. H₂O
C₇H₁₀O₃N₂ (170.1) calc'd: C 49.40; H 5.92%
found: C 49.44; H 5.56%

Diethyl 3,4-Dimethyl-5,6-dihydro-1,2-pyran-6,6-dicarboxylate (XXI)

Diethyl mesoxalate (20 g.) mixed with dimethylbutadiene (11 g.) and hydroquinone (0.5 g.) was refluxed for 4 hours in a flask protected against moisture. After removal of the unchanged material by distillation at the water pump, the addition product was purified by fractionation in high vacuo. Pale yellow oil, b. p. 107—108°/0.5 mm. (15 g., 52%).

Anal. 19.64 mg. subst.: 43.40 mg. CO₂, 13.42 mg. H₂O
C₁₃H₂₀O₅ (256.3) calc'd: C 60.92; H 7.87%
found: C 60.36; H 7.65%

3,4-Dimethyl-5,6-dihydro-1,2-pyran-6,6-dicarboxylic acid diamide (XXII) prepared from the diethyl ester XXI formed opaque leaflets, m.p. 269–270° (from aqueous solution). On admixture with the diamide XIV, the melting point remained undepressed.

Anal. 23.65 mg. subst.: 2.979 ml. N₂ (22°, 732.98 mm.)
C₉H₁₄O₃N₂ (198.2) calc'd: N 14.13%
found: N 13.88%

The authors are indebted to Mrs. F. Werner-Zamojska for the microanalyses.

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IZVOD

Kemizam karbonil cijanida. Dienofilna svojstva karbonil cijanida i dietilnog estera mezoksalne kiseline. Stvaranje dihidropiranskih derivata

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Opisane su reakcije karbonil cijanida s butadienom i 2,3-dimetil butadienom. U oba slučaja dolazi do dienske kondenzacije i do stvaranja odgovarajućih dihidropiranskih derivata. Derivati dihidropirana dobiveni su i kondenzacijom dietilnog estera mezoksalne kiseline s dienima. Strukture adicijonih spojeva određene su degradacionim reakcijama.

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Primljeno 13. lipnja 1957.