3-Carbalkoxy-4-diazo-5-oxo-2-pyrrolines

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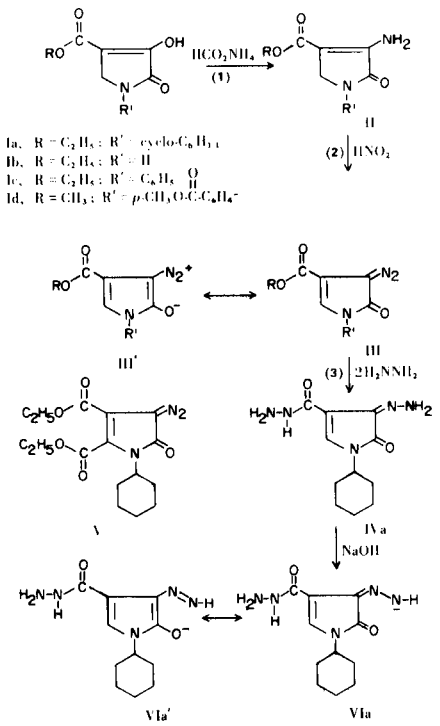
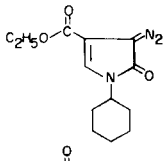
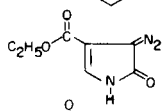
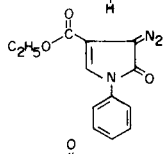
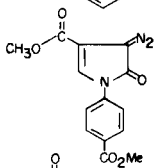
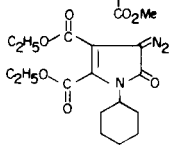
The enolic 4-carboalkoxy-2,3-dioxopyrrolidines (I) are easily converted (equation (1)), into 3-amino-4-carboalkoxy-3-pyrrolin-2-ones (II) by treatment with ammonium formate in refluxing ethanol (1) or cellosolve (2). It became of interest to determine how compounds of type II, which are enamines of considerable stability, would respond to treatment with nitrous acid. One result considered as a possibility was the formation of diazonium salts. In the event, however, diazotization caused migration of the olefinic bond of the pyrroline ring accompanying formation of a diazo function, as shown in equation (2). Conversion to the 4-diazo-2-pyrroline derivatives (III) *via* the 3-amino-3-pyrroline derivatives (II) was carried out with the four enolic 4-carboalkoxy-2,3-dioxopyrrolidines (Ia-Id). The 2,3-dicarbethoxy derivative V, related to the compounds of type III, was obtained in a similar way from 1-cyclohexyl-4,5-dicarbethoxy-2,3-dioxopyrrolidine.

The products exhibited strong infrared absorption near



4.7 μ, indicative of a diazo group (3a) and an unsplit one-proton signal in the nmr spectrum at *ca.* 3.2 τ, consistent with a hydrogen on a vinyl carbon attached to nitrogen and incorporated into a conjugated system. These data, as well as elemental analyses and the other features of the spectra, appeared to rule out any structure but III for these compounds. They were clearly not ionic diazonium chlorides (diazotizations were conducted in hydrochloric acid) and could be regarded as containing the diazonium group only to the degree that zwitterions such as III might contribute to resonance in such a structure (3a,b,c). These diazo derivatives appeared to be thermally stable and less reactive toward many reagents than typical diazo compounds or diazonium salts. The cyclohexyl derivative IIIa was recovered unchanged after it had been refluxed in benzene or treated with acetic acid at room temperature. Coupling did not appear to occur with *N,N*-dimethylaniline or β-naphthol. The formation of biologically active triazenes from such similar heterocyclic diazo derivatives as 5-diazoimidazole-4-carboxamide (4) prompted an investigation of the action of amines on compound IIIa. Experiments with diethylamine, however, yielded unchanged diazo compound. In contrast, treatment with hydrazine in refluxing ethanol resulted in a clean reaction and permitted the separation of a crystalline product, m.p. 208-210°, although in rather low yield. Reaction began with a rather brisk evolution of gas (possibly nitrogen) at room temperature. The composition of the product, as indicated both by chemical analysis and by the exact mass of the parent ion (251.1380) obtained from the mass spectrum, was $C_{11}H_{17}N_5O_2$. The infrared spectrum indicated the introduction of one or more $-NH_2$ groups (bands at *ca.* 3.1 and 3.2 μ) and the removal of the diazo group (no remaining band at 4.74 μ). A one-proton singlet was seen in the nmr spectrum at τ 1.40. A structure which would be consistent with this information would be that of the hydrazide hydrazone IVa, formed by reaction of IIIa with two moles of hydrazine as in equation (3). The only observation not immediately explained by structure IVa was solubility observed in aqueous sodium hydroxide. Possible stabilization resulting from the opportunity for charge delocalization in a derived anion *via* a contribution from an aroma-

Table I

No.	Structure	Yield, %	M.p.	Analytical Data: Calculated C	Calculated H	Calculated N	Found C	Found H	Found N
IIIa		53.6	94-95° (a)	59.29	6.51	15.96	59.42	6.64	15.76
IIIb		59.5	126-127°	46.41	3.89	23.19	46.39	3.98	23.44
IIIc		35.4	76-77°	60.69	4.31	16.34	60.78	4.08	16.22
IIId		58.8	148-149°	55.82	3.68	13.95	55.77	3.64	13.79
V		69.3	65-66°	57.30	6.31	12.53	57.36	6.39	12.35

(a) Ir (Nujol): μ 4.74 (>C=N=N), 5.95 (ester C=O), 6.10 (shoulder, C=C), 6.40, 7.32, 7.50, 7.76, 8.0. Nmr (deuteriochloroform): τ 8.65 (t, 3H, J = 7 Hz, OCH_2CH_3), 7.80-8.8 (m, 10H of cyclohexyl), 5.8-6.0 (m, 1H, methine of cyclohexyl), 5.54-5.90 (q, 2H, J = 7 Hz, $-OCH_2CH_3$) 3.18 (s, 1H, proton at 5-position).

tized pyrrole structure VIa′ could account for such a degree of acidity in a structure of type IV. The behavior of IIIa in its reaction with hydrazine contrasts with that of 5-diazoimidazole-4-carboxamide and related diazoimidazoles, pyrazoles and 1,2,3-triazoles, which have recently been shown to yield azido derivatives with hydrazine and some derived reagents (5).

One of the compounds, the *p*-carbomethoxy derivative IIId ($R' = p\text{-}CH_3\text{-}O\text{-}\overset{O}{\overset{\|}{C}}\text{-}C_6H_4\text{-}$) showed some activity against a rhinovirus strain in an *in vitro* assay (6).

EXPERIMENTAL (7)

4-Carbomethoxy-1-(*p*-carboxyphenyl)-2,3-dioxopyrrolidine.

To a flask equipped with a magnetic stirrer and condenser was added *p*-aminobenzoic acid (109.6 g., 0.8 mole), methyl acrylate (292 ml., 3.2 moles), and glacial acetic acid (292 ml.). The resulting mixture was refluxed with stirring for 9 hours and then evaporated to dryness under reduced pressure on a steam bath. The intermediate β-aminopropionate was collected by filtration and washed repeatedly with ether until traces of methyl acrylate and acetic acid could no longer be detected. The air-dried β-aminopropionate, methyl oxalate (94.4 g., 0.8 mole), and 1 l. of absolute methanol were added to a 3-liter flask equipped with a mechanical stirrer and condenser. To the resulting stirred mixture was added a solution of sodium methoxide (1.6 moles, 36.8 g. of sodium metal in 400 ml. of absolute methanol). After heating at reflux for 30-45 minutes the reaction mixtures noticeably thickened, frequently stopping the stirrer. Stirring was restarted, when necessary, by adding additional methanol and heating was continued for an additional hour. The mixture was then acidified with 800 ml. of 20% hydrochloric acid, and the solid was collected by filtration and thoroughly washed with water, acetone, and finally ether. Drying in air yielded a white powder, 122.3 g. (0.44 mole, 55%), m.p. 277-279° dec. The product was used in subsequent reactions without further purification. However, recrystallization could be achieved from dimethylformamide to give short, white, needles, m.p. 283-286° dec. Spectra: ir (Nujol): 3.00 (enolic, O-H), 3.43, 3.50, 3.75, 3.93, 5.85 (ester and acid, C=O), 5.96 (lactam, C=O), 6.15, 6.21 (aromatic, C=C), 6.34, 6.49, 6.59 (aromatic, C=C), 6.83, 6.92, 6.99, 7.07, 7.18, 7.27, 7.34, 7.56, 7.67, 7.79, 8.00 μ; nmr (deuterium oxide-sodium carbonate): 6.37 (s, 3H, ester-CH_3), 6.07 (s, 2H, 5-CH_2), 2.32 τ (AB system, J = 8.5 Hz, 4H, aromatic).

Anal. Calcd. for $C_{13}H_{11}NO_6$: C, 56.31; H, 4.00; N, 5.05. Found: C, 56.48; H, 3.97; N, 5.01.

4-Carbomethoxy-1-(*p*-carbomethoxyphenyl)-2,3-dioxopyrrolidine (Id).

A 2-liter flask equipped with a dropping funnel, condenser, and mechanical stirrer was charged with 30.0 g. (0.108 mole) of 4-carbomethoxy-1-(*p*-carboxyphenyl)-2,3-dioxopyrrolidine and 500 ml. of absolute methanol. Acetyl chloride (45 ml., 1 ml. for each 20 ml. of methanol) was added carefully, with stirring, from the dropping funnel, and the mixture was refluxed for 3 hours. The

flask was then cooled in an ice bath and the dimethyl ester was collected by filtration and washed with water, methanol, and ether. Drying in a vacuum desiccator then gave 31.0 g. (0.106 mole, 98%) of fluffy white powder, m.p. 225-229° dec. Recrystallization from dimethylformamide-acetone yielded colorless needles, m.p. 229-231° dec. The product gave a red ferric chloride test. Spectra: ir (Nujol): 2.89 (enol, O-H), 3.00, 3.38, 5.81 (ester, C=O), 5.93 (lactam, C=O), 6.21 (aromatic, C=C), 6.62 (aromatic, C=C), 6.86, 6.90, 7.03, 7.11, 7.20, 7.32, 7.38, 7.58, 7.70, 7.80, 7.84, 7.90, 8.00 μ; nmr (TFA): 5.96 (s, 3H, ester-CH_3), 5.93 (s, 3H, ester-CH_3), 5.32 (s, 2H, 5-CH_2), 1.95 τ (q, J = 9.0 Hz, 4H, aromatic).

Anal. Calcd. for $C_{14}H_{13}NO_6$: C, 57.73; H, 4.50; N, 4.82. Found: C, 57.86; H, 4.62; N, 4.73.

3-Amino-4-carbomethoxy-1-(*p*-carbomethoxyphenyl)-2-oxo-3-pyrroline (IId).

A mixture of 25 g. (0.086 mole) of 4-carbomethoxy-1-(*p*-carbomethoxyphenyl)-2,3-dioxopyrrolidine, 50 g. (0.793 mole) of ammonium formate, and 450 ml. of 2-ethoxyethanol was refluxed for 24 hours. The mixture became homogeneous and magnetic stirring was begun shortly after refluxing commenced. At the end of the reaction period, the deep red-orange colored solution was cooled in an ice bath for several hours and the product was collected by filtration. After washing with water, 95% ethanol, absolute ethanol, and ether, the product was dried in a vacuum desiccator to give 20.5 g. (70.6 mmoles, 82.1%) of beige-colored microcrystalline powder, m.p. 208-212° dec. Following recrystallization from dioxane (with decolorization by charcoal in some runs) the product was obtained as short, colorless needles, m.p. 218-220° dec. The product gave only a yellow color with ferric chloride. Spectra: ir (Nujol): 2.78 (N-H), 2.88 (N-H), 3.40, 5.88 (ester, C=O), 6.07 (lactam, C=O), 6.21 (aromatic, C=C), 6.45 (N-H), 6.61 (aromatic, C=C), 6.89, 7.07, 7.24, 7.31, 7.58, 7.75, 7.81, 7.99 μ; nmr (TFA): 5.96 (s, 3H, ester-CH_3), 5.90 (s, 3H, ester-CH_3), 5.32 (s, 2H, 5-CH_2), 1.93 τ (q, J = 9.5 Hz, 4H, aromatic).

Anal. Calcd. for $C_{14}H_{14}N_2O_5$: C, 57.93; H, 4.86; N, 9.65. Found: C, 57.86; H, 5.07; N, 9.76.

3-Amino-4-carbethoxy-1-cyclohexyl-2-oxo-3-pyrroline (IIa).

A mixture prepared from 40.5 g. (0.16 mole) of 4-carbethoxy-1-cyclohexyl-2,3-dioxopyrrolidine (8), 20.0 g. (0.32 mole) ammonium formate, and 200 ml. of absolute ethanol was refluxed for 24 hours and the solvent was evaporated under reduced pressure. The residue was slurried with 100 ml. of water and collected by filtration. After drying in air, the product was decolorized by dissolving it in 300 ml. of 95% ethanol and treating the solution with charcoal. The charcoal was removed with Celite filter aid and the solution was concentrated and cooled to yield 35.35 g. (0.14 mole, 87.5%) of the IIa as colorless rods, m.p. 151.5-153.5° dec. Nmr (deuteriochloroform): 8.70 (t, J = 7.5 cps, 3H, ester-CH_3), 8.22 (m, 10H, cyclohexyl), 6.10 (s, 2H, 5-CH_2), 5.77 (q, J = 7.0 cps, 2H, ester-CH_2), 4.03 τ (s, 2H, 3-NH_2).

Anal. Calcd. for $C_{13}H_{20}N_2O_3$: C, 61.88; H, 7.99; N, 11.10. Found: C, 61.90; H, 8.06; N, 11.02.

3-Amino-1-cyclohexyl-4,5-dicarbethoxy-2-oxo-2-pyrroline.

A solution of 1-cyclohexyl-4,5-dicarbethoxy-2,3-dioxopyrrolidine (9) (10.0 g.) and ammonium formate (15.0 g.) in 35 ml. of 2-ethoxyethanol was refluxed for 20 hours. The mixture was poured onto ice, and the product was collected by filtration, washed with water, and recrystallized from ethanol following decolorization with charcoal. The yield was 7.3 g. (71.6%), m.p. 111-112°.

Anal. Calcd. for $C_{16}H_{24}N_2O_5$: C, 59.24; H, 7.46; N, 8.64. Found: C, 59.40; H, 7.55; N, 8.58.

3-Amino-4-carbethoxy-4-phenyl-2-oxo-3-pyrroline (IIc).

A solution of 4-carbethoxy-1-phenyl-2,3-dioxopyrrolidine (10) (5 g.) and ammonium formate (7 g.) in 20 ml. of 2-ethoxyethanol was refluxed for 12 hours, then poured into water. The product was collected by filtration and crystallized from ethanol; yield 3.9 g. (78.3%), m.p. 123-124°.

Anal. Calcd. for $C_{13}H_{14}N_2O_5$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.40; H, 5.48; N, 11.08.

3-Carboalkoxy-4-diazo-5-oxo-2-pyrrolines (III).

The procedure for preparation of compound IIIb given below was applied without any significant changes to the preparation of all of the diazo derivatives of type III. Yields and data on these compounds are given in Table I.

To a stirred suspension of 1.5 g. of 3-amino-4-carbethoxy-2-oxo-3-pyrroline (1) in a mixture of glacial acetic acid and concentrated hydrochloric acid (12 ml.:4 ml.) at ice-salt bath temperature, a saturated solution of sodium nitrite (8 ml.) was added dropwise. The solution was basified by addition of concentrated aqueous ammonia at 0.5°. The brown solid obtained was collected by filtration, washed with a little cold water and crystallized from ethanol to give 0.95 g. (59.5%) of 3-carbethoxyl-4-diazo-5-oxo-2-pyrroline, m.p. 126-127°.

Reaction of 1-Cyclohexyl-4-diazo-3-carboethoxy-5-oxo-2-pyrroline with Hydrazine.

The diazo derivative IIIa (1.0 g.) was dissolved in 15 ml. of absolute ethanol and 5 ml. of 100% hydrazine hydrate was added dropwise. Evolution of gas bubbles was observed. The mixture was raised to the reflux temperature. The original orange color of the solution of IIIa faded to light yellow a few minutes after heating was begun. After a 2-hour reflux period the solution was cooled. A crystalline solid (150 mg., m.p. 208-210°) separated and was collected by filtration. Recyrstallization from ethanol did not change the m.p. The substance dissolved readily in aqueous sodium hydroxide, but not in aqueous sodium bicarbonate. It dissolved slowly in aqueous sodium carbonate. Spectra: ir (Nujol): μ 3.01, 3.15 (N-H), 6.05 (lactam C=O), 6.15, 6.40, 6.53, 6.75, 7.40, 7.75, 8.01; nmr (deuteriochloroform-TFA = 3.2 v/v) τ 7.75-8.8 (m, 10H of cyclohexyl) 6.00-6.30 (1H, methine of cyclohexyl), 1.41 (s, 1H, proton at 5-position).

Anal. Calcd. for $C_{11}H_{17}N_5O_2$: C, 52.57; H, 6.82; N, 27.87; mole wt., 251.1382. Found: C, 52.20; H, 7.39; N, 28.39; mole wt. (parent ion of mass spectrum), 251.1380. (The slightly unsatisfactory elemental analysis is unexplained by the nmr results or the mass spectrum.).

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μ band shows that our derivatives have not cyclized in such a fashion; (c) The analogy between these compounds and the so-called diazo oxides or diazo phenols (derived by diazotization of *o* or *p*-aminophenols) has been pointed out by a referee. See, for example, K. H. Saunders, "The Aromatic Diazo Compounds and Their Technical Application," Second Ed., Longmans, Green & Co., New York, N.Y., 1949, p. 28.

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(7) Microanalyses are by M-H-W Laboratories, Garden City, Michigan. Melting points were determined with a Mel-Temp apparatus in capillary tubes and are corrected. Where infrared data for compounds are given, all major bands below 8.0 μ are included. Nmr spectra were determined with a Perkin-Elmer-Hitachi R-20 instrument; solvents used were deuterium oxide, deuteriohcloroform and trifluoroacetic acid (TFA): signals are quoted at τ values, with s indicating singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Mass spectra were determined on an AEI-MS9 high resolution mass spectrometer; the authors are indebted to J. R. Boal for determination and interpretation of such spectra.

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