Tetraoxo Derivatives of Perhydropyrrolo[3,4-*c*]pyridine (1)

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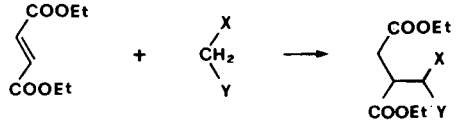
Michael adducts from diethyl fumarate with malonic esters or nitriles were cyclized to succinimide intermediates which, after glutarimide ring closure, afforded several *N*-methyl and *N*-benzyl derivatives of *cis*-1,3,4,6-tetraoxoperhydropyrrolo[3,4-*c*]pyridine whose configuration was demonstrated by X-ray crystal structure analysis.

J. Heterocyclic Chem., **20**, 439 (1983).

In a previous paper (2), the synthesis of some oxo derivatives of furo[3,4-*c*]pyran, furo[3,4-*c*]pyridine and pyrrolo[3,4-*c*]pyran, prepared by cyclizing Michael adducts from *trans*-diacetylethylene with acetoacetic esters was described. The analogous ring system with two nitrogen atoms, *i.e.* pyrrolo[3,4-*c*]pyridine was not obtained during that investigation, due to poor reactivity of the intermediates.

Although the pyrrolo[3,4-*c*]pyridine ring system is already known (3,4) also in partially hydrogenated forms (4,5,6,7), it was felt that derivatives with one or more carbonyl groups (4,5,8,25) might show interesting properties as purine or xanthine analogues. We thus decided to synthesize polyoxo derivatives of fully hydrogenated pyrrolo-[3,4-*c*]pyridine through cyclization of Michael adducts from diethyl fumarate with malonic esters or nitriles, so as to obtain a fused succinimide-glutarimide ring system **4**. Michael additions of diethyl malonate and ethyl cyanoacetate to diethyl fumarate affording tetraester **1a** and cyanoester **1b**, respectively, had already been described (9,10,11). We have now obtained an additonal adduct, *i.e.* the dicyanoester **1c** from diethyl fumarate with malonitrile.



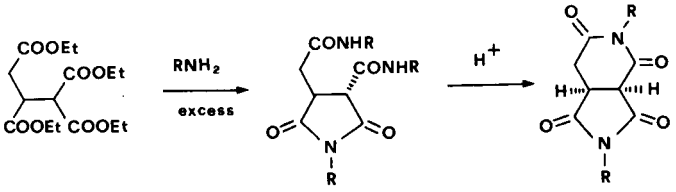
1

a : X = Y = -COOEt

b : X = -COOEt ; Y = -CN

c : X = Y = -CN

Tetraester **1a** was known to react with excess aqueous ammonia to give an imide-diamide whose supposed structure **3a** had not been demonstrated (9). However, we were



1a 3 4

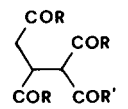
a : R = H-

b : R = CH_3-

c : R = C_6H_5-CH_2-

able to confirm its succinimide structure which was consistent both with the formation conditions (glutarimides are not stable in excess aqueous ammonia (12,13)) and with the ir spectrum showing characteristic carbonyl absorptions of five-membered imides at 1770 and 1730 cm^{-1} (14); furthermore, a value of 6 Hz for the ring vicinal proton coupling constant from nmr spectrum, suggested a *trans* configuration of the substituents (15).

By reacting tetraester **1a** with an excess of methylamine in dioxane, we obtained the tri-*N*-methyl-derivative **3b**, whereas excess of benzylamine (neat) gave a complex reaction mixture: tetra-*N*-benzylamide **2a** as the major product and small amounts of the tri-*N*-benzyl derivative **3c** and amidoester **6c**, whose structural assignment was made by analogy with other amidoesters **6** prepared by partial



2

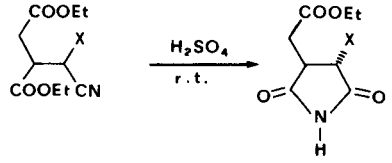
a : R = R' = C_6H_5-CH_2NH-

b : R = EtO- ; R' = NH_2-

amidation of **5** (see below). Evidence for a *trans* disubstituted succinimide structure of **3b,c** and **6c** was the same as mentioned for **3a**.

Treatment of **3a** with *p*-toluenesulfonic acid in refluxing xylene produced 1,3,4,6-tetraoxoperhydropyrrolo[3,4-*c*]-pyridine (**4a**) as a moderately unstable product, in very poor yield. Nevertheless, both the diamides **3b** and **c**, the amidoester **6c**, as well as tetramide **2a**, were easily cyclized by treatment with *p*-toluenesulfonic acid in refluxing xylene, to the corresponding bicyclic diimides 2,5-dimethyl-1,3,4,6-tetraoxoperhydropyrrolo[3,4-*c*]pyridine (**4b**) and 2,5-dibenzyl-1,3,4,6-tetraoxoperhydropyrrolo[3,4-*c*]-pyridine (**4c**), respectively.

In order to prepare unsymmetrically substituted derivatives of pyrrolo[3,4-*c*]pyridine **4**, as well as the unsubstituted **4a** in a better yield, nitrile adducts **1b,c** were submitted to acidic imide cyclization (16). Concentrated sulfuric acid at room temperature converted **1b** into the imidodiester **5a** and **1c** into imidoamidoester **6a**. In the case of **1b**, the acyclic amide **2b** was also isolated. This could, however, be cyclized to **5a** by refluxing in trifluoroacetic



1

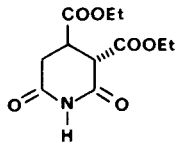
b : X = -COOEt 5 a : X = -COOEt

c : X = -CN 6 a : X = -CONH$_2$

acid.

Since acidic reagents can cyclize cyano-esters to either succinimides or glutarimides (13,16,17,18), evidence of the succinimide nature of the ring in compounds **5a** and **6a** was required. Both ir spectrum (presence of high frequency carbonyl absorption: 1770 and 1780 cm^{-1} respectively) and the moderate stability in aqueous base, clearly indicated the presence of a succinimide ring; furthermore the similarity of skeletal nmr pattern of both compounds to that of **3a, b, c**, confirmed the analogy and again showed a *trans* configuration of the substituents.

An imidodiester, isomeric with **5a**, was obtained by treating **1b** with sulfuric acid in refluxing acetic acid (16). Its ir spectrum did not show the high frequency carbonyl absorption characteristic of the succinimide ring and its treatment with aqueous base produced immediate hydrolysis and in addition, its nmr spectrum showed a different skeletal pattern. All of these properties were consistent with the glutarimide structure **7**. A *trans* configuration was assigned on the basis of the value (9 Hz) of the coupling constant between the two protons α with respect to the ester groups, in analogy with *trans* diaxial protons in half

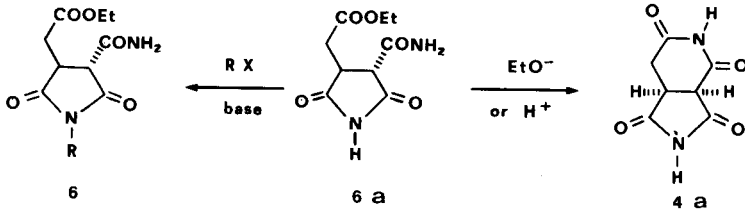


7

chair six-membered rings containing carbonyl groups (19).

The amidoester **6a** was easily cyclized to unsubstituted 1,3,4,6-tetraoxoperhydropyrrolo[3,4-*c*]pyridine (**4a**) in either basic (sodium ethoxide in ethanol) or acidic (*p*-toluenesulfonic acid in refluxing xylene) conditions. These results suggested the route to afford *N,N'*-unsymmetrically substituted derivatives of **4a** by using various *N*-methyl or *N*-benzyl derivatives of **6a** as intermediates. These compounds were produced by two different kinds of reactions, or their combination, *i.e.* alkylation of succinimide nitrogen in structures **5** and **6** and selective amidation of one ester group in structures **5**.

Alkylation of **6a** with methyl iodide in basic medium easily gave **6e**. The same reaction was not performed on **5a** because the bicyclic products obtainable from the intermediate methyl derivative were more easily produced by other routes.



6 6 a 4 a

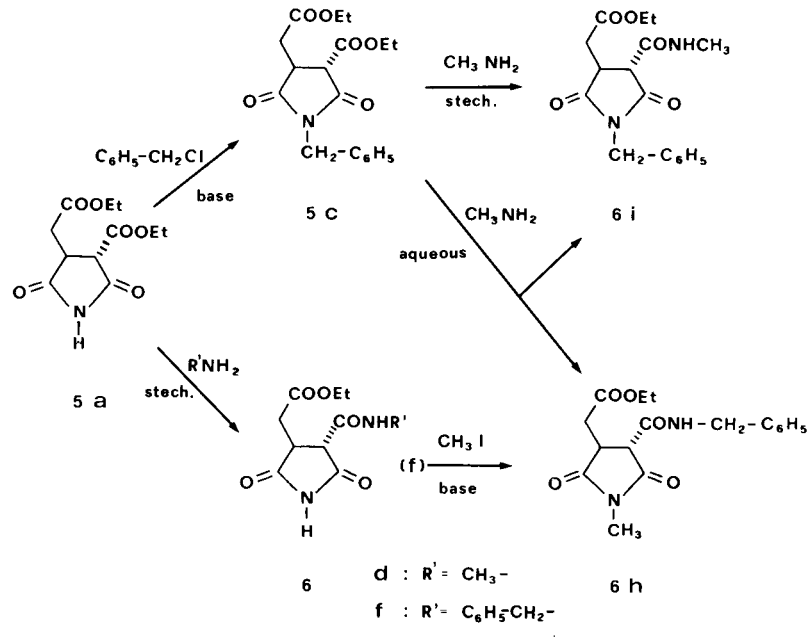
e : R = -CH$_3$

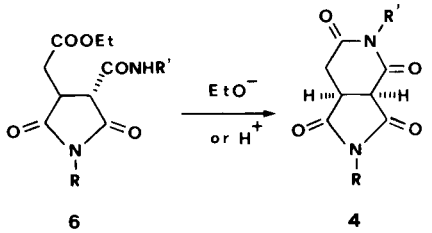
g : R = C$_6$H$_5$-CH$_2$-

Treatment of both **5a** and **6a** with benzyl chloride in basic medium produced reaction mixtures of monobenzylated (**5c** and **6g**, respectively) and dibenzylated products. The latter were shown to be N_1,C_3-dibenzyl derivatives of the 2,5-dioxopyrrolidine ring (**8a** and **8b**, respectively) by nmr analysis. Compounds **8a,b** were apparently formed by *C*-alkylation of the malonic carbanion, probably by an SN_1 mechanism since no similar behaviour was observed with methyl iodide.

Treatment of **5a,c** with one mole of methylamine or benzylamine in dioxane solution resulted in a remarkable regioselective amidation. A single amidoester was always isolated (**6d,f** from **5a**; **6i** from **5c**), which retained the original succinimide structure.

Evidence as to which of the two ester groups had reacted was derived from nmr chemical shift comparison with diesters **5a,c** and the amidoester **6a** and was also occasionally confirmed when, by reacting **5c** with aqueous





6c : R = R' = $C_6H_5-CH_2-$: 4c
6d : R = H- ; R' = CH_3- : 4d
6e : R = CH_3- ; R' = H- : 4e
6f : R = H- ; R' = $C_6H_5-CH_2-$: 4f
6g : R = $C_6H_5-CH_2-$; R' = H- : 4g
6h : R = CH_3- ; R' = $C_6H_5-CH_2-$: 4h
6i : R = $C_6H_5CH_2-$; R' = CH_3- : 4i

methylamine, the isomeric compound **6h** was also isolated together with the expected **6i**. Compound **6h** can be formed through a rearrangement only consistent with amidoester structures **6** and not with isomeric ones.

Selective amidation at the 3-ester group was probably due to a strong -I inductive effect of the nearby imidic group, which enhanced the electrophilic character of the carbonyl in the 3-ester group with respect to the carbonyl in the 4-ester group. By the mentioned alkylation and amidation reactions, a complete series of unsymmetrically *N*-substituted succinimidoesteramides **6d-i** was produced. These compounds could, in principle, cyclize under both acidic or basic conditions to give the corresponding unsymmetrically N_2,N_5-substituted 1,3,4,6-tetraoxoperhydropyrrolo[3,4-*c*]pyridines **4d-i**. In the experimental, best conditions for optimum yields are reported, showing basic cyclization to be somewhat preferable for primary amides (20).

The question as to whether retention of the *trans* configuration or its rearrangement to a *cis* configuration had occurred under the cyclization conditions was not easily resolved by nmr analysis. The rather high value (9 Hz) of the ring junction proton coupling constant in the whole series of structures **4** (Table IV) was consistent either with a *cis*-disubstituted succinimide (15) or with a *trans* α,β-disubstituted glutarimide (19). We then decided to undertake a crystallographic analysis on one member of the structures **4** in order to verify the ring junction configuration.

Crystallographic data referring to structure **4d** are reported in the experimental section and a stereochemical view of the molecule is shown in Figure 1, clearly indicating a *cis*-junction of the two rings.

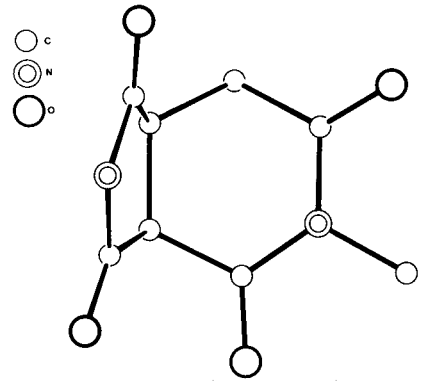
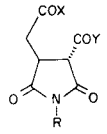


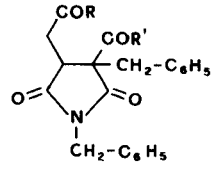
Figure 1. A stereochemical view of 5-methyl-1,3,4,6-tetraoxoperhydropyrrolo[3,4-*c*]pyridine (**4d**).

Table I

Physical and Analytical Data of Succinimide Intermediates



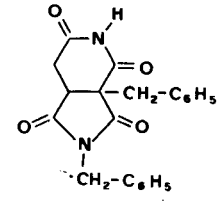
Compound No.	R	X	Y	Mp (°C) Solvent (s)	Formula	Analysis % Calcd./Found C	H	N
3b	CH_3-	CH_3NH-	CH_3NH-	224-225 (Water)	$C_{10}H_{15}N_3O_4$	49.78 49.97	6.27 6.16	17.42 17.48
3c	$C_6H_5CH_2$-	$C_6H_5CH_2NH$-	$C_6H_5CH_2NH$-	180-182 (Acetone)	$C_{28}H_{27}N_3O_4$	71.62 71.28	5.80 5.84	8.95 8.77
5a	H-	C_2H_5O-	C_2H_5O-	85-87 (Water)	$C_{11}H_{15}NO_6$	51.36 51.30	5.88 6.01	5.45 5.30
5c	$C_6H_5CH_2$-	C_2H_5O-	C_2H_5O-	oil	$C_{18}H_{21}NO_6$	62.24 62.19	6.10 6.41	4.03 3.90
6a	H-	C_2H_5O-	NH_2-	127-128 (Chloroform)	$C_9H_{12}N_2O_5$	47.37 47.06	5.30 5.31	12.28 11.99
6c	$C_6H_5CH_2$-	C_2H_5O-	$C_6H_5CH_2NH$-	127-128 (Methanol)	$C_{23}H_{24}N_2O_5$	67.63 67.36	5.92 5.88	6.86 6.71
6d	H-	C_2H_5O-	CH_3NH-	154-156 (Chloroform-hexane)	$C_{10}H_{14}N_2O_5$	49.58 49.52	5.83 6.06	11.57 11.42
6e	CH_3-	C_2H_5O-	NH_2-	112-113 (Acetone)	$C_{10}H_{14}N_2O_5$	49.58 49.65	5.83 6.01	11.57 11.41
6f	H-	C_2H_5O-	$C_6H_5CH_2NH$-	109-111 (Chloroform-hexane)	$C_{16}H_{18}N_2O_5$	60.37 60.07	5.70 5.64	8.80 8.52
6g	$C_6H_5CH_2$-	C_2H_5O-	NH_2-	112-114 (Chloroform-hexane)	$C_{16}H_{18}N_2O_5$	60.37 60.26	5.70 5.95	8.80 8.83
6h	CH_3-	C_2H_5O-	$C_6H_5CH_2NH$-	124-126 (Methanol)	$C_{17}H_{20}N_2O_5$	61.43 61.54	6.07 6.05	8.43 8.27
6i	$C_6H_5CH_2$-	C_2H_5O-	CH_3NH-	115-117 (Chloroform-hexane)	$C_{17}H_{20}N_2O_5$	61.43 61.74	6.07 5.96	8.43 8.32



8

a : R = R' = EtO-

b : R = EtO- ; R' = NH_2-



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The similarity of skeletal nmr pattern of compounds **4** speaks for the same configuration in the whole series. This means that, in all cyclization conditions used, inversion of one asymmetric carbon occurs, thus converting the *trans*-disubstituted succinimide into a *cis*-disubstituted intermediate whose glutarimide ring closure affords structure **4**. An explanation of this behaviour could be found in the lesser steric strain in the *cis*-fused succinimide ring, as compared with a *trans*-fused one.

The unsubstituted diimide **4a** as its methyl derivatives **4b,d,e** could be regarded as structural analogues of a purine or xanthine nucleus. Similarly, the monobenzyl derivatives **4f,g,h,i** could be regarded as covalently bound analogues (21,22) of a nucleic base pair in which the benzene ring could simulate a pyrimidine base. Unfortunately, the *cis*-junction of the two imide rings makes the bicyclic nucleus of structures **4** nonplanar, thus partly destroying the analogy.

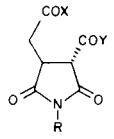
EXPERIMENTAL

Melting points were determined by capillary method on a dr. Tottoli (Büchi) apparatus and are uncorrected. Elemental analyses were performed by Dr. A. Reho using a Hewlett-Packard 180-CHN-analyzer.

The ir spectra (not reported) were fully consistent with the proposed structures. The nmr spectra were taken on a Varian EM-360, 60 MHz spectrometer using TMS as the internal standard. The following abbreviations were used: s, singlet (s); d, doublet; t, triplet; dt, double

Table II

NMR (a) Spectra of Succinimide Intermediates



Compound No.	R	X	Y	NMR, δ (ppm), J = Hz
3b	CH_3-	CH_3NH-	CH_3NH-	2.40-2.65 (m, 8H, two C*H*$_3$NH + CH_2, partially masked), 2.82 (s, 3H, CH_3N), 3.13 (q, 1H, 4-CH, J = 5), 3.48 (d, 1H, 3-CH, J = 5), 7.85 (s, br, 1H, NH), 8.23 (s, br, 1H, NH)
3c	$C_6H_5CH_2$-	$C_6H_5CH_2NH$-	$C_6H_5CH_2NH$-	2.55-3.10 (m, 2H, CH_2CO), 3.25-3.50 (m, 1H, 4-CH), 3.85 (d, 1H, 3-CH, J = 6), 4.23 (d, 2H, C*H*$_2$NH, J = 6), 4.36 (d, 2H, C*H*$_2$NH, J = 6), 4.60 (s, 2H, CH_2N), 6.07 (t, 1H, NH), 7.24 (m, 15H, aromatics), 7.42 (t, 1H, NH)
5a	H-	C_2H_5O-	C_2H_5O-	1.23 and 1.32 (2t, 6H, CH_3, J = 7), 2.84 (d, 2H, CH_2CO, J = 6), 3.56 (q, 1H, 4-CH, J = 6, partially masked), 3.69 (d, 1H, 3-CH, J = 6), 4.10 and 4.24 (2q, 4H, CH_2O, J = 7), 10.32 (s, br, 1H, NH)
5c	$C_6H_5CH_2$-	C_2H_5O-	C_2H_5O-	1.22 and 1.34 (2t, 6H, CH_3, J = 7), 2.95 (d, 2H, CH_2CO, J = 6), 3.52 (q, 1H, 4-CH, J = 6), 3.75 (d, 1H, 3-CH, J = 6), 4.15 and 4.35 (2q, 4H, CH_2O, J = 7), 4.77 (s, 2H, CH_2N), 7.43 (s, 5H, aromatics)
6a	H-	C_2H_5O-	NH_2-	1.16 (t, 3H, CH_3, J = 7), 2.50-2.95 (m, 2H, CH_2CO), 3.05-3.35 (m, 1H, 4-CH), 3.39 (d, 1H, 3-CH, J = 6), 4.00 (q, 2H, CH_2O, J = 7), 7.26 and 7.65 (s, br, 2H, NH_2), 11.34 (s, br, 1H, NH)
6c	$C_6H_5CH_2$-	C_2H_5O-	$C_6H_5CH_2NH$-	1.13 (t, 3H, CH_3, J = 7), 2.60-3.25 (m, 2H, CH_2CO), 3.35-3.55 (m, 1H, 4-CH), 3.62 (d, 1H, 3-CH, J = 6), 3.96 (q, 2H, CH_2O, J = 7), 4.20-4.50 (m, 2H, C*H*$_2$NH, partially masked), 4.45-4.80 (m, 2H, CH_2N, partially masked), 7.25 (m, 11H, 10H, aromatics + NH)
6d	H-	C_2H_5O-	CH_3NH-	1.16 (t, 3H, CH_3C, J = 7), 2.30-2.90 (m, 5H, CH_3N, + CH_2CO, partially masked), 3.00-3.65 (m, 2H, CH-CH), 4.08 (q, 2H, CH_2O, J = 7), 8.20 (s, br, 1H, N*H*-CH_3), 11.45 (s, br, 1H, NH)
6e	CH_3-	C_2H_5O-	NH_2-	1.28 (t, 3H, CH_3-C, J = 7), 2.70-3.25 (m, 2H, CH_2CO), 3.05 (s, 3H, CH_3N), 3.25-3.55 (m, 1H, 4-CH), 3.66 (d, 1H, 3-CH, J = 6), 4.11 (q, 2H, CH_2O, J = 7), 6.00 and 7.04 (s, br, 2H, NH_2)
6f	H-	C_2H_5O-	$C_6H_5CH_2NH$-	1.20 (t, 3H, CH_3, J = 7), 2.60-3.30 (m, 2H, CH_2CO), 3.35-3.85 (m, 2H, CH-CH), 4.10 (q, 2H, CH_2O, J = 7), 4.46 (d, 2H, CH_2N, J = 5), 7.32 (s, 6H, 5H aromatics + N*H*CH_2), 9.16 (s, 1H, NH)
6g	$C_6H_5CH_2$-	C_2H_5O-	NH_2-	1.18 (t, 3H, CH_3, J = 7), 2.65-3.35 (m, 2H, CH_2CO), 3.40-3.65 (m, 1H, 4-CH), 3.72 (d, 1H, 3-CH, J = 5), 4.11 (q, 2H, CH_2O, J = 7), 4.71 (s, 2H, CH_2N), 5.82 and 7.04 (s, br, 2H, NH_2), 7.35 (s, 5H, aromatics)
6h	CH_3-	C_2H_5O-	$C_6H_5CH_2NH$-	1.18 (t, 3H, CH_3C, J = 7), 2.65-3.10 (m, 2H, CH_2CO, partially masked), 2.92 (s, 3H, CH_3N), 3.30-3.80 (m, 2H, CH-CH), 4.15 (q, 2H, CH_2O, J = 7), 4.45 (d, 2H, CH_2N, J = 5), 7.38 (s, 5H, aromatics), 8.90 (t, 1H, NH)
6i	$C_6H_5CH_2$-	C_2H_5O-	CH_3NH-	1.20 (t, 3H, CH_3C, J = 7), 2.87 (d, 3H, CH_3N, J = 5), 2.90-3.30 (m, 2H, CH_2CO, partially masked) 3.35-3.75 (m, 2H, CH-CH), 4.11 (q, 2H, CH_2O, J = 7), 4.73 (s, 2H, CH_2N), 7.10 (s, br, 1H, NH), 7.38 (s, 5H, aromatics)

(a) All spectra were recorded in dimethyl sulfoxide-d_6; the proton in the 3-position was exchanged by deuterium oxide addition: the intensity of its signal was sometimes lower than expected, possibly due to partial enolization.

Table III

Physical and Analytical Data of *cis*-1,3,4,6-Tetraoxoperhydropyrrolo[3,4-*c*]pyridines **4**

Compound No.	R	R'	Yield %	Mp (°C) (Solvent)	Formula	Analysis % Calcd./Found C	H	N
4a	H-	H-	72	255-260 dec (Methanol)	$C_7H_6N_2O_4$	46.16 45.88	3.32 3.62	15.38 15.08
4b	CH_3-	CH_3-	50	207-209 (Water)	$C_9H_{10}N_2O_4$	51.42 51.74	4.80 5.02	13.33 13.46
4c	$C_6H_5CH_2$-	$C_6H_5CH_2$-	48 (from **3c**) 25 (from **6c**)	215-217 (Ethanol)	$C_{21}H_{18}N_2O_4$	69.60 69.65	5.00 5.00	7.73 7.68
4d	H-	CH_3-	40	239-241 (Ethanol)	$C_8H_8N_2O_4$	48.98 48.68	4.11 4.41	14.28 14.21
4e	CH_3-	H-	68	178-180 (Ethanol)	$C_8H_8N_2O_4$	48.98 49.02	4.11 4.01	14.28 14.10
4f	H	$C_6H_5CH_2$-	45	164-165 (Methanol)	$C_{14}H_{12}N_2O_4$	61.76 61.51	4.44 4.20	10.29 10.03
4g	$C_6H_5CH_2$-	H-	40	202-205 (Ethanol)	$C_{14}H_{12}N_2O_4$	61.76 62.06	4.44 4.49	10.29 10.35
4h	CH_3-	$C_6H_5CH_2$-	80	145-147 (Ethanol)	$C_{15}H_{14}N_2O_4$	62.93 63.04	4.93 5.01	9.79 9.72
4i	$C_6H_5CH_2$-	CH_3-	70	173-175 (Ethanol)	$C_{15}H_{14}N_2O_4$	62.93 62.71	4.93 4.82	9.79 9.73

Table IV

NMR (a) Spectra of *cis*-1,3,4,6-Tetraoxoperhydropyrrolo[3,4-*c*]pyridines **4**

Compound No.	R	R'	NMR, δ (ppm), J = Hz
4a	H-	H-	2.55-2.95 (m, 2H, CH_2), 3.10-3.55 (m, 1H, 7a-CH), 3.84 (d, 1H, 3a-CH, J = 9), 11.20 (s, br, 2H, NH)
4b	CH_3-	CH_3-	2.84 (s, 3H, 2-CH_3), 2.92 (d, 2H, CH_2, partially masked), 2.97 (s, 3H, 5-CH_3), 3.42 (dt, 1H, 7a-CH, J = 9, J = 6), 4.05 (d, 1H, 3a-CH, J = 9)
4c	$C_6H_5CH_2$-	$C_6H_5CH_2$-	2.80-3.20 (m, 2H, CH_2CO), 3.35-3.70 (m, 1H, 7a-CH), 4.24 (d, 1H, 3a-CH, J = 9), 4.50 (s, 2H, 2-CH_2N), 4.75 (s, 2H, 5-CH_2N), 7.20 (m, 10H, aromatics)
4d	H-	CH_3-	2.78 (d, 2H, CH_2, partially masked), 2.95 (s, 3H, CH_3), 3.40 (dt, 1H, 7a-CH, J = 9, J = 6), 4.02 (d, 1H, 3a-CH, J = 9), 11.55 (s, br, 1H, NH)
4e	CH_3-	H-	2.82 (d, 2H, CH_2, partially masked), 2.86 (s, 3H, CH_3), 3.60 (dt, 1H, 7a-CH, J = 9, J = 6), 3.97 (d, 1H, 3a-CH, J = 9), 11.14 (s, br, 1H, NH)
4f	H-	$C_6H_5CH_2$-	3.00 (d, 2H, CH_2CO), 3.63 (dt, 1H, 7a-CH, J = 9, J = 6), 4.17 (d, 1H, 3a-CH, J = 9), 4.83 (s, 2H, CH_2N), 7.28 (s, 5H, aromatics), 11.60 (s, br, 1H, NH)
4g	$C_6H_5CH_2$-	H-	2.60-3.20 (m, 2H, CH_2CO), 3.40-3.80 (m, 1H, 7a-CH), 4.07 (d, 1H, 3a-CH, J = 9), 4.57 (s, 2H, CH_2N), 7.30 (s, 5H, aromatics), 11.10 (s, br, 1H, NH)
4h	CH_3-	$C_6H_5CH_2$-	2.86 (s, 3H, CH_3), 3.05 (d, 2H, CH_2CO), 3.53 (dt, 1H, 7a-CH, J = 9, J = 6), 4.21 (d, 1H, 3a-CH, J = 9), 4.83 (s, 2H, CH_2N), 7.28 (s, 5H aromatics)
4i	$C_6H_5CH_2$-	CH_3-	2.95 (d, 2H, CH_2CO), 2.98 (s, 3H, CH_3), 3.59 (dt, 1H, 7a-CH, J = 9, J = 6), 4.23 (d, 1H, 3a-CH, J = 9), 4.58 (s, 2H, CH_2N), 7.30 (s, 5H, aromatics)

(a) All spectra were recorded in dimethyl sulfoxide-d_6, the proton in the 3-position was exchanged by deuterium oxide addition: the intensity of its signal was sometimes lower than expected, possibly due to the partial enolization.

triplet; q, quartet; m, multiplet (s); br, broad signal. Exchange with deuterium oxide was used to identify N-H protons. Chromatographic separations were carried out on silica gel columns (0.06-0.2 mm, Merck). Physical, analytical and spectroscopic data of 2,5-dioxopyrrolidine derivatives **3b,c**, **5a,c**, **6a,c-i** and of bicyclic compounds **4a-i** are reported in Tables I, II, III, IV.

3,3-Dicyano-1,2-propanedicarboxylic Acid Diethyl Ester (**1c**).

Malonitrile (9.9 g, 0.15 mole) in ethanol (15 ml) was added dropwise to an ice-cooled solution of sodium ethoxide (8.17 g, 0.12 mole) in ethanol (50 ml) under mechanical stirring. The mixture was then allowed to warm to room temperature and ethyl fumarate (13.9 ml, 0.126 mole) was added dropwise over a period of about 15 minutes. The neutralized (acetic acid) solution was evaporated to dryness and the residue was partitioned in water and carbon tetrachloride. The organic layer was dried (sodium sulfate), and evaporated to dryness and distilled under reduced pressure to give 22.5 g (75% yield) of **1c** bp 147-149°/2 mm Hg; nmr (deuteriochloroform): δ 1.30 and 1.34 (2t, 6H, CH_3, J = 7 Hz), 2.60-3.20 (m, 2H, CH_2-CO), 3.54 (q, 1H, CH-CO, J = 6 Hz), 4.18 and 4.28 (2q, 4H, CH_2-O, J = 7 Hz), 4.51 (d, 1H, CH-CN, J = 6 Hz).

Anal. Calcd. for $C_{11}H_{14}N_2O_4$: C, 55.45; H, 5.92; N, 11.76. Found: C, 55.70; H, 6.05; N, 11.88.

trans-3,4-Dicarbethoxypiperidine-2,6-dione (**7**).

A solution of **1b** (1 g, 3.5 mmoles) in glacial acetic acid (18 ml) and concentrated sulfuric acid (2 ml) was refluxed for 0.5 hour. After cooling the reaction mixture was poured on ice, the *p*H adjusted to 6 with sodium carbonate and the solution extracted with chloroform. After drying (sodium sulfate) the solvent was eliminated and the residue crystallized from acetone-hexane to give 0.31 g (34% yield) of **7**, mp 95-97°; nmr (deuterioacetone): δ 1.25 and 1.28 (2t, 6H, CH_3, J = 7 Hz), 2.60-3.05 (m, 2H, CH_2CO), 3.35-3.75 (m, 1H, 4-CH), 3.89 (d, 1H, 3-CH, J = 9 Hz), 4.14 and 4.20 (2q, 4H, CH_2O, J = 7 Hz), 9.88 (s, br, 1H, NH).

Anal. Calcd. for $C_{11}H_{15}NO_6$: C, 51.36; H, 5.88; N, 5.44. Found: C, 51.44; H, 6.13; N, 5.44.

trans-3-Carbethoxy-4-carbethoxymethylpyrrolidine-2,5-dione (**5a**).

A solution of **1b** (8.65 g, 30 mmoles) in concentrated sulfuric acid (9 ml) was stirred at room temperature for 24 hours and then poured on ice. The *p*H was adjusted to 6 with sodium carbonate, the solution extracted with chloroform and the organic layer dried (sodium sulfate), evaporated to dryness and the residue washed several times with a diluted solution of sodium hydroxide. The aqueous alkaline solution was rapidly acidified with hydrochloric acid and extracted with chloroform. The organic layer was dried (sodium sulfate) and evaporated to dryness to give 4.24 g (55% yield) of **5a**. The residue insoluble in sodium hydroxide (3.64 g, 40% yield) was identified as **2b**, mp 72-73° from benzene-hexane; nmr (deuteriochloroform): δ 1.23 (t, 3H, CH_3, J = 7 Hz), 1.26 (t, 6H, -CH_3 J = 7 Hz), 2.55-2.80 (m, CH_2-CO), 3.30-3.60 (m, 1H, C*H*-CH_2), 3.77 (d, 1H, C*H*-$CONH_2$, J = 7 Hz), 4.09 (q, 6H, CH_2-O, J = 7 Hz), 6.70 and 7.15 (s, br, 2H, NH_2).

Anal. Calcd. for $C_{13}H_{21}NO_7$: C, 51.48; H, 6.98; N, 4.62. Found: C, 51.36; H, 7.18; N, 4.47.

Compound **2b** was converted to **5a** by refluxing in trifluoroacetic acid.

trans-3-Aminocarbonyl-4-carbethoxymethylpyrrolidine-2,5-dione (**6a**).

Concentrated sulfuric acid (10 ml) was added dropwise to nitrile **1c** (9.53 g, 40 mmoles) during a period of about 3 hours by heating at 40-50° with magnetic stirring. After 20 hours the reaction mixture was cooled, poured on ice and sodium carbonate was added to adjust *p*H to about 6. The aqueous solution was extracted with chloroform and the organic layer dried (sodium sulfate) and concentrated until precipitation of **6a** (4.56 g, 50% yield) occurred.

trans-3-Methylaminocarbonyl-4-methylaminocarbonylmethyl-1-methylpyrrolidine-2,5-dione (**3b**).

A solution of tetraester **1a** (10 g, 30.1 mmoles) and methyl amine (11.2 g, 0.36 moles) in anhydrous dioxane (100 ml) was stirred at room temperature for 24 hours. The precipitate was collected, washed with ethanol and crystallized to give 4.43 g (61% yield) of **3b**.

trans-3-Benzylaminocarbonyl-4-benzylaminocarbonylmethyl-1-benzylpyrrolidine-2,5-dione (**3c**).

Tetraester **1a** (10 g, 30.1 mmoles) was refluxed for 4 hours in benzylamine (39.4 ml, 0.36 moles). The precipitate was collected, washed with diluted hydrochloric acid and then with hot acetone. The acetone solution was chromatographed on silica gel column (methylene chloride-ethyl acetate 80/20 as eluent) to give 0.74 g (6% yield) of **6c** as first fraction and 2.82 g (20% yield) of **3c** as second fraction. The residue insoluble in hot acetone (2.08 g, 12% yield) was identified as 1,1,2,3-propanetetracarboxylic acid tetrabenzylamide **2a**, mp 270-272° (not crystallized); nmr (trifluoroacetic acid): δ 2.85-3.10 (m, 2H, CH_2-CO), 3.65-4.00 (m, 1H, C*H*-CH_2), 4.04 (d, 1H, C*H*-CH-CH_2, J = 5 Hz), 4.10-4.60 (m, 8H, four CH_2-N), 7.28 (m, 20H aromatics), 7.83 (s, br, 2H, NH), 8.14 (s, br, 1H, NH), 8.40 (s, br, 1H, NH).

Anal. Calcd. for $C_{35}H_{36}N_4O_4$: C, 72.89; H, 6.29; N , 9.72. Found: C, 72.59; H, 6.27; N, 9.38.

Compound **2a** was converted into **3c** or **4c** by refluxing in trifluoroacetic acid or in xylene containing *p*-toluenesulfonic acid, respectively.

trans-3-Methylaminocarbonyl-4-carbethoxymethylpyrrolidine-2,5-dione (**6d**) and *trans*-3-Methylaminocarbonyl-4-carbethoxymethyl-1-benzylpyrrolidine-2,5-dione (**6i**).

A solution of **5a** or **5c** (10 mmoles) and methylamine (.342 g, 11 mmoles) in anhydrous dioxane (80 ml) was heated in a sealed tube at 110° for 24 hours. After removing the solvent the residue was crystallized to give 1.1 g of **6d** (45% yield) or 1.9 g of **6i** (57% yield). Upon treatment with aqueous methylamine in ethanol at room temperature **5c** produced both **6i** and **6h**.

trans-3-Benzylaminocarbonyl-4-carbethoxymethylpyrrolidine-2,5-dione (**6f**).

A solution of **5a** (1.29 g, 5 mmoles) and benzylamine (0.60 ml, 5.5 mmoles) in dioxane (50 ml) was refluxed for 15 hours. The residue obtained after removal of the solvent was crystallized to give 1.19 g (75% yield) of **6f**.

trans-3-Carbethoxy-4-carbethoxymethyl-1-benzylpyrrolidine-2,5-dione (**5c**) and *trans*-3-Aminocarbonyl-4-carbethoxymethyl-1-benzylpyrrolidine-2,5-dione (**6g**).

Benzyl chloride (1.15 ml, 10 mmoles) was added dropwise to a solution of **5a** (or **6a**) (10 mmoles) and finely powdered potassium hydroxide (0.56 g, 10 mmoles) in anhydrous dimethyl sulfoxide (25 ml) with magnetic stirring. After 3 hours, the reaction mixture was diluted with water and extracted with chloroform. The organic layer was washed with water, dried (sodium sulfate), evaporated to dryness and chromatographed on a silica gel column using ethyl acetate-petroleum ether as eluent (30/70 and 60/40 for **5a** and **6a**, respectively). From **5a** were obtained 2.1 g (60% yield) of **5c** as the first fraction, and 0.66 g (15% yield) of **8a** (analytically pure oil) as the second fraction; nmr (deuteriochloroform): δ 1.20 and 1.35 (2t, 6H, CH_3, J = 7 Hz), 2.20-3.20 (m, 2H, C*H*$_2$-CH), 3.35-3.70 (m, 3H, C-C*H*$_2$-C_6H_5 + CH), 4.23 and 4.30 (2q, 4H, CH_2-O, J = 7 Hz), 4.68 (s, 2H, CH_2N), 7.34 (s, 10H, aromatics).

Anal. Calcd. for $C_{25}H_{27}NO_6$: C, 68.63; H, 6.22; N, 3.20. Found: C, 68.26; H, 6.34; N, 3.01.

From **6a** three fractions were obtained in the following sequence: 1.43 g of **6g** (45% yield), 0.53 g of **8b** (13% yield), 0.22 g of **9** (6% yield), **8b**, mp 109-111° from acetone-water; nmr (deuteriochloroform): δ 1.18 (t, 3H, CH_3, J = 7 Hz), 2.60-3.60 (m, 5H, CH_2-CH + C_6H_5-C*H*$_2$-C), 3.85 (q, 2H, CH_2O, J = 7 Hz), 4.46 (s, 2H, CH_2-N), 5.80 (s, br, 1H, NH), 7.00 (s, 5H aromatics), 7.17 (s, 6H, 5H aromatics + NH).

Anal. Calcd. for $C_{23}H_{24}N_2O_5$: C, 67.63; H, 5.92; N, 6.86. Found: C, 67.32; H, 5.64; N, 6.79.

Compound **9** had mp 191-193° from water-ethanol; nmr (DMSO-d_6): δ 2.60-3.00 (m, 2H, CH_2-CO), 3.40-3.80 (m, 3H, C_6H_5-C*H*$_2$-C + CH), 4.62 (s,

2H, CH_2N), 7.30 (m, 10H aromatics), 11.30 (s, br, 1H, NH).

Anal. Calcd. for $C_{21}H_{18}N_2O_4$: C, 69.60; H, 5.01; N, 7.73. Found: C, 69.72; H, 5.32; N, 7.73.

trans-3-Aminocarbonyl-4-carbethoxymethyl-1-methylpyrrolidin-2,5-dione (**6e**) and *trans*-3-Benzylaminocarbonyl-4-carbethoxymethyl-1-methylpyrrolidine-2,5-dione (**6h**).

A solution of **6a** (or **6f**) (10 mmoles), finely powdered potassium hydroxide (0.56 g, 10 mmoles) and methyl iodide (0.62 ml, 10 mmoles) in absolute ethanol (40 ml) was stirred at room temperature for 24 hours. After removing the solvent the residue was partitioned in chloroform and water, the organic layer dried (sodium sulfate), and evaporated to dryness afforded 1.40 g of **6e** (58% yield) or 2.36 g of **6h** (71% yield).

Ring Closure of Intermediates **3** and **6** to *cis*-1,3,4,6-Tetraoxoperhydropyrrolo[3,4-*c*]pyridines **4**.

a) A solution of sodium ethoxide (0.51 g, 7.5 mmoles) in absolute ethanol (5 ml) was added dropwise to a solution of **6a** 1.71 g (7.5 mmoles) in the same solvent (30 ml) at room temperature with magnetic stirring. After 16 hours the precipitate was collected and dissolved in the minimum amount of diluted hydrochloric acid from which **4a** immediately crystallized as a moderately unstable product (0.98 g, 72% yield).

b) A suspension of **6g** (0.95 g, 3 mmoles) and finely powdered sodium hydroxide (0.48 g, 12 mmoles) in anhydrous dioxane (75 ml) was refluxed for 6 hours. After cooling the solution was neutralized with hydrochloric acid, diluted with water and extracted with chloroform. The organic layer was dried (sodium sulfate) and concentrated until precipitation of **4g** (0.31 g, 38% yield) occurred.

c) A solution of tetramide **2a** or diamide (**3b,c**) or amidoester (**6c,d,e,f,h,i**) (10 mmoles) and *p*-toluenesulfonic acid hydrate (1.9 g, 10 mmoles) in anhydrous xylene (40 ml) was refluxed in a nitrogen atmosphere for 12 hours. After removal of the solvent under reduced pressure and crystallization, the title bicyclic compounds were obtained in the yields reported in Table II.

Crystal Structure Analysis of 5-Methyl-1,3,4,6-tetraoxoperhydropyrrolo-[3,4-*c*]pyridine (**4d**).

Suitable single crystals for an X-ray structure analysis were obtained by slow evaporation from an ethanol solution of compound **4d**. The crystal data are the following: $C_8H_8N_2O_4$, F.W. 196.16; monoclinic, space group $P2_1/c$ from systematic absences; a = 11.227(5), b = 6.177(1), c = 12.828(5) Å, β = 111.68(3)°, V = 826.7 Å^3, Z = 4, D_c = 1.57 g.cm.$^{-3}$, D_o = 1.57 g.cm.$^{-3}$ by flotation in chloroform and bromoform, λ (MoKα) = 0.71069 Å, μ(MoKα) = 1.38 mm^{-1}. The intensities of 2430 independent reflections (2 ϑ max = 58.0°) were measured by the $\vartheta - 2\vartheta$ scan technique on a Syntex $P2_1$ automatic four-circle diffractometer equipped with graphite monochromator and MoKα radiation: 1501 out of them were considered observed [$I > 2.6\sigma(I)$] and used in the refinement. The structure was solved by direct methods using the MULTAN '78 program (23). The final difference Fourier synthesis revealed acceptable atomic positions for all the hydrogen atoms. The structure was anisotropically refined by full-matrix least-squares methods for all the non hydrogen atoms, whereas the hydrogen atom parameters were kept fixed with isotropic thermal values assumed from the carrier atoms.

The final R and R_w are 0.064 and 0.102 respectively. All the calculations were carried out on the HP 21MX minicomputer (24) of the CNR Research Area and on the UNIVAC 1100/80 computer of the University of Rome.

As can be deduced from Figure 1 where a stereochemical view on the mean plane of six-membered ring of the molecule is shown, the fusion between the five-membered and the six-membered rings is of the *cis*-type and therefore the overall shape of the molecule is bent.

Full details of the moleculear crystal structure will be given elsewhere.

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