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α,β-UNSATURATED CARBOXYLIC ACID DERIVATIVES. 20.[1] N-METHYLATION OF α-DEHYDROAMINO ACID ESTER AND ITS CYCLIC DIPEPTIDE FROM VARIOUS ROUTES

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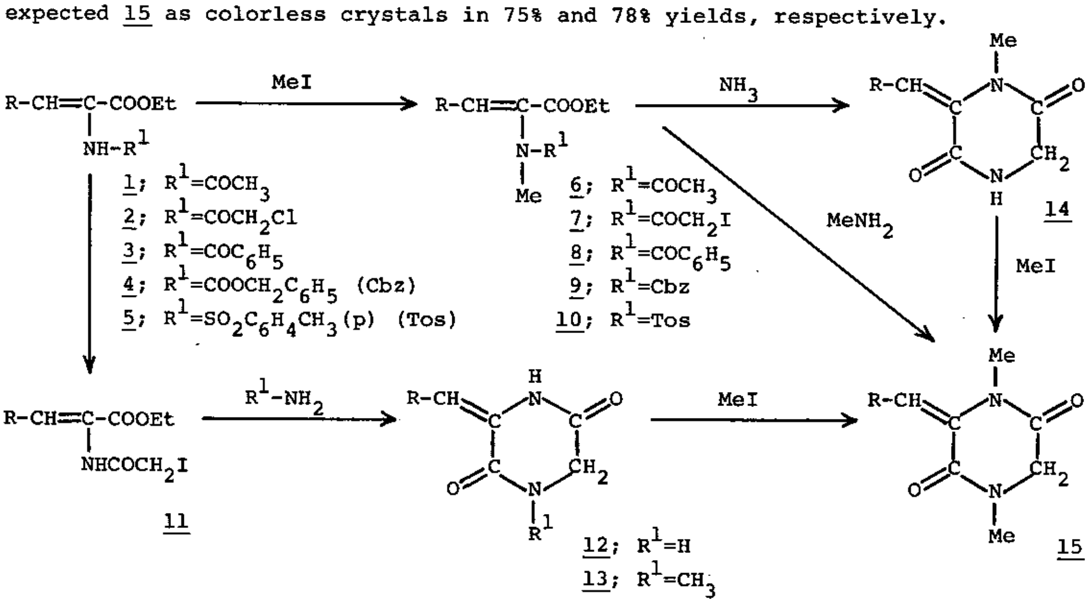
Abstract——The selective N-methylation of 1-, 4-, and 1,4-positions of individual 3- and 3,6-dialkylidene-2,5-piperazinediones (PDO) either by the cyclization of α-dehydroamino acid ester with methylamine or by the reaction of PDO with methyl iodide in the presence of sodium hydride was performed to give the desired product in a fairly good yield.

Recently, many bioactive oligopeptides N-blocked partially with methyl group were discovered and the correlation between the structure and the bioactivity of the peptides has been investigated.[2,3] Furthermore, antibiotic N-methylated dehydropeptides such as tentoxin[4] were isolated, a few of which were synthesized.[5-7] The useful N-methylation of α-amino acid and peptide has been almost established by the several methods,[8-11] but that of α-dehydroamino acid (DHA) and dehydropeptide (DHP) has not yet been investigated thoroughly. Because of more lability of DHA and DHP and of restriction, e. g., hydrolysis and geometric isomerization,[12] under currently employed procedures, it is necessary to establish the optimal conditions for the N-methylation of the various DHA and DHP.

In this paper, we wish to report on the synthesis of several N-methylated N-acyl-, N-benzyloxycarbonyl (Cbz)-, and N-(p)-toluenesulfonyl (Tos)-DHA esters (1-5) by the method of Rich et al[7] and the various synthetic routes for the selective methylation at 1-, 4-, and 1,4-positions of 3- and 3,6-dialkylidene-2,5-piperazinediones (PDO) by the reaction of PDO with methyl iodide[13] and by the cyclization of DHA with methylamine. Moreover, 1-, 4-, and 1,4-dimethylated albonoursin, antibiotic albonoursin from the culture filtrate of Streptomyces noursei[14] and S. thioluteus[15] and its two analogs were also prepared here.

The reaction of the starting (Z)-2-N-substituted DHA esters[16-18] (1-5; 18.7 mmol) with 5 moles of methyl iodide and K_2CO_3 in DMF (50 ml) at room temperature for 48 hr was carried out to give the desired N-methylated DHA esters (6-10) in a ca. 84% yield. In the case of 2, it was found that the halogen exchange between chlorine and iodine occurred to give (Z)-2-(N-methyl)iodoacetyl derivative (7). Subsequently, according to the usual method,[17] the compound 7 (14.2 mmol) thus obtained was cyclized with gaseous ammonia in methanol (30 ml) to give colorless crystals, identified as 4-methyl-3-(Z)-alkylidene-PDO (14), in a 71% yield. On the other hand, 1-methyl isomer of 14 (13) was obtained as colorless crystals in an almost quantitative yield by the cyclization of ethyl (Z)-2-iodoacetyl-2-alkenoate (11; 5.57 mmol) with 3 moles of methylamine (made from $MeNH_2 \cdot HCl$ and sodium) in methanol (30 ml) at room temperature for 2 hr.

Furthermore, the preparation of 1,4-dimethyl-3-alkylidene-PDO (15) was pursued from the possible four synthetic routes successfully. The individual 13 and 14 (7.92 mmol) reacted readily with an equimolar amount of sodium hydride and 1.2 moles of methyl iodide (9.50 mmol) at room temperature for 1 hr to give the expected 15 as colorless crystals in 75% and 78% yields, respectively.



a; R=CH_3, b; R=C_2H_5, c; R=i-C_3H_7, d; R=C_6H_5

Scheme 1

Table 1. Yields, physical constants, and spectral data of 6-10

Compound No.	Yield (%)	Mp °C	IR spectrum, cm^{-1} c) COOEt	NCO	C=C	NMR spectrum, δ in $CDCl_3$ -CH= (J_{Hz})	$N-CH_3$
6d	91	48-50 a)	1720	1670	1630	7.64	3.08
7b	81	syrup	1735	1680	1655	7.05 (7.5)	3.08
7c	84	syrup	1740	1680	1650	6.82 (10.5)	3.06
7d	81	syrup	1725	1670	1635	7.68	3.13
8d	86	107-108 a)	1720	1670	1640	7.20-7.70 d)	3.26
9c	79	syrup	1725	1710	1650	6.58 (10.5)	3.07
10c	84	syrup	1735		1650	6.81 (10.0)	2.99
10d	83	126-128 b)	1720		1640	7.25-7.84 d)	3.12

a) Colorless prisms from hexane. b) Colorless prisms from AcOEt. c) Recorded in KBr. d) Overlapped on phenyl protons.

Table 2. Yields, physical constants, and spectral data of 13-16

Compound No.	Yield (%)	Mp °C	IR spectrum, cm^{-1} in KBr NH	C=O		C=C	NMR spectrum, δ in $CDCl_3$ (* in CF_3COOH) -CH= (J_{Hz})	$N-CH_3$	NH ($COCH_3$)
13a	97	249-251 d)	3200	1680	1675	1635	6.63 (7.5)	3.28	9.88*
13b	91	133-134 e)	3200	1705	1690	1650	6.14 (7.5)	3.06	9.34
13c	91	187-189 e)	3200	1690	1680	1640	6.04 (10.0)	3.06	9.08
13d	98	147-148 f)	3200	1705	1685	1645	6.96	3.04	8.16
14b	71	89.5-90.5 g)	3180	1700	1660	1645	6.10 (7.5)	3.26	8.09
14c	68	144-146 h)	3225	1700	1665	1645	6.00 (11.0)	3.29	7.98
14d	75	176-177 h)	3300	1700		1635	7.20	2.91	8.10
15b	82 a)	syrup		1700	1690	1640	6.16 (7.5)	3.03 3.27	
15c	80 b)	111-112 i)		1690	1665	1640	6.03 (11.0)	3.04 3.29	
15d	86 c)	112-113 g)		1695		1630	7.30	2.90 3.11	
16a	98	syrup		1720	1690	1650	6.10 (10.0)	3.25	(2.55)
16b	93	161-163 f)		1710 1700	1690	1615	7.38	2.96	(2.65)

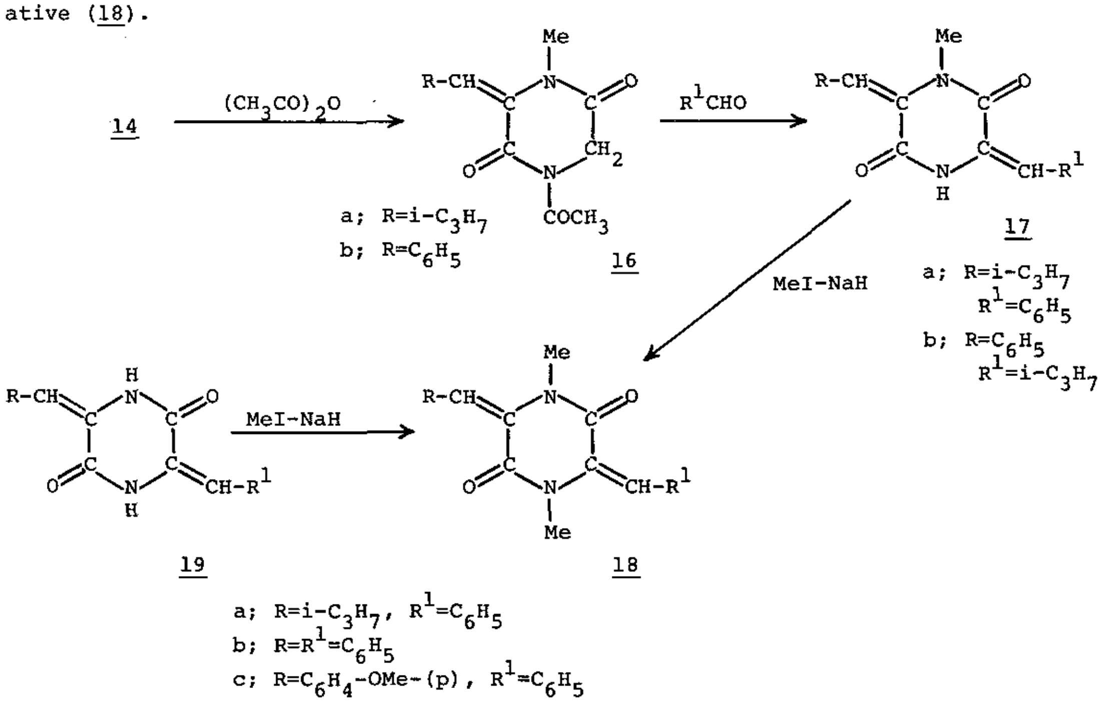
a) Yield from 12. 69% from 7, 70% from 13. b) Yield from 12. 67% from 7, 65% from 13, 64% from 14. c) Yield from 12. 83% from 7, 91% from 13, 92% from 14. d) Colorless needles from H_2O. e) Colorless prisms from AcOEt. f) Colorless needles from EtOH. g) Colorless needles from benzene-hexane. h) Colorless needles from AcOEt. i) Colorless needles from dibutyl ether.

On the other hand, compound 15 was also obtained in 73% and 83% yields, respectively, by cyclization of 7 with methylamine and by methylation of 3-alkylidene-PDO (12)[17] with methyl iodide in a similar manner as above.

The yields, physical constants, and spectral data of 6-10 and 13-15 are summarized in Tables 1 and 2, respectively.

From NMR spectral data of 13-15 and by comparison with the (E)-isomer of 12,[19] the comparatively lower chemical shifts of the exocyclic olefinic protons appeared at δ 6.00-7.30 region show unambiguously 13-15 to have (Z)-geometric structure. Therefore, the geometry of the starting olefins as well as the product (15) thus obtained was found to be maintained as (Z)-configurational structure.

Furthermore, for the condensation of 14 with aldehyde, the acetylation of 14 (12.4 mmol) with acetic anhydride (14 ml) was carried out under reflux for 2 hr to give 1-acetyl-4-methyl-3-alkylidene-PDO (16) quantitatively. The condensation of 16 (3.49 mmol) with 5 moles of appropriate aldehyde in t-butanol in the presence of 0.5M potassium t-butoxide (3.49 mmol) gave 4-methyl-3,6-dialkylidene-PDO (17) as colorless crystals in a ca. 52% yield. Further methylation of 17 (6.67 mmol) with 1.2 moles of methyl iodide (8.0 mmol) and an equimolar sodium hydride was worked up similarly to give the corresponding 1,4-dimethyl derivative (18).



Scheme 2

On the other hand, albonoursin [3-(Z)-isobutylidene-6-(Z)-benzylidene-PDO][20-22] and its two naturally occurring analogs [3-(Z)-, 6-(Z)-dibenzylidene-PDO and 3-(Z)-p-anisilidene-6-(Z)-benzylidene-PDO] (19)[15,23,24] were subjected to the direct methylation. As in the case of 13 and 14, compound 19 was worked up similarly with methyl iodide and sodium hydride to give 18 in a ca. 73% yield, which was in complete agreement with one obtained from 17.

In consequence, the structurally interesting 1-, 4-, and 1,4-dimethyl derivatives of albonoursin and its two analogs could be prepared here.

The yields, melting points, and spectral data of 17 and 18 are listed in Table 3. Especially, in order to compare two olefin and methine protons between albonoursin[22] and the other N-methylated analogs, the structure of four compounds are illustrated in Figure 1.

Table 3. Yields, physical constants, and spectral data of 17 and 18

Compound			Yield (%)		Mp °C	IR spectrum, cm^{-1} in KBr				NMR[h)]	
No.	R	R^1	A[a)]	B[b)]		NH	C=O	C=C		$N-CH_3$	NH
17a	$i-C_3H_7$	C_6H_5	51		142-143[e)]	3150	1690	1630	1615	3.38	8.30
17b	C_6H_5	$i-C_3H_7$	52		165-166[e)]	3160	1680	1640	1620	2.99	9.70
18a	$i-C_3H_7$	C_6H_5	62[c)] 74[d)]	72	125-126[f)]	—	1690	1630		2.90 3.37	—
18b	C_6H_5	C_6H_5		77	138-139[g)]	—	1680 1660	1615		3.00	—
18c	C_6H_4-OMe-p	C_6H_5		70	140-142[e)]	—	1685	1620		3.00 3.05	—

a) Yield from 17. b) Yield from 19. c) Yield from 17a. d) Yield from 17b.
e) Colorless needles from dibutyl ether. f) Colorless needles from hexane.
g) Colorless needles from diethyl ether. h) NMR spectrum, δ in $CDCl_3$.

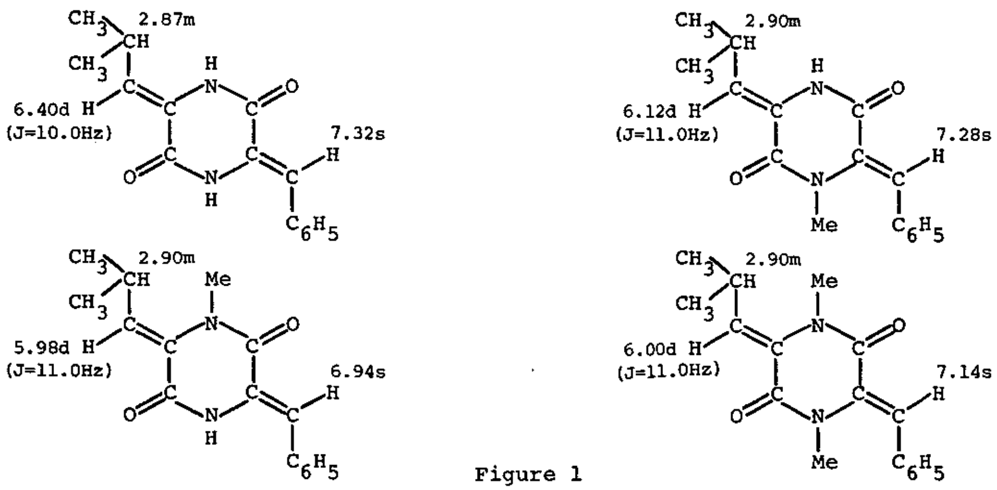


Figure 1

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