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Chemistry of Amino Acids. VII.[1] The Synthesis and Spectral Studies of Some 2-Piperidones bearing β-Keto Ester Groups

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Some 2-piperidones (IX and X) bearing β-keto ester groups were synthesized from the methyl esters (V) of alanine and phenylalanine according to a route similar to that described in our previous paper.[3] Spectral studies (infrared, ultraviolet and nuclear magnetic resonance) revealed that these β-keto esters (IX and X) mainly exist in the chelated enolic tautomer (E) both in the solid state and in solution. The NMR spectra of some indole derivatives[3] (XI—XVI) were also investigated.

In an early paper[3] from our laboratory, we described the synthesis of the vobasine skeleton (IV) from tryptophan (I), based upon the Dieckmann condensation of dimethyl esters (II) to some 2-piperidone derivatives (III). Interesting spectral properties of III, which bear β-keto ester groups, were also reported.

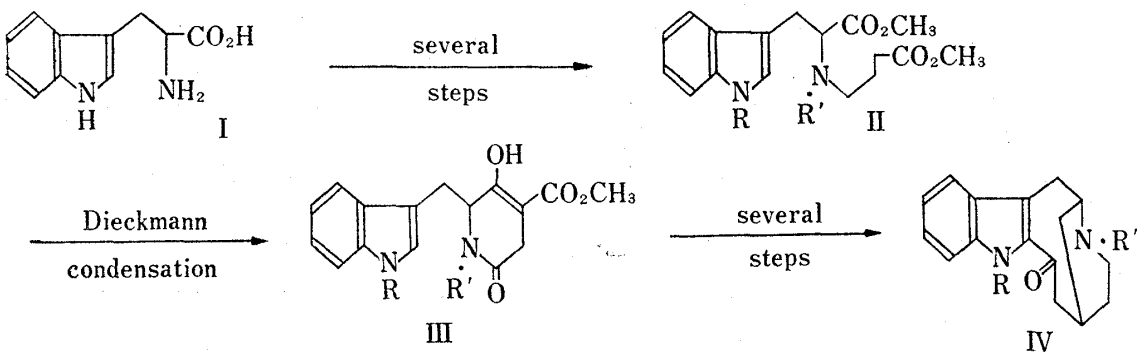


Chart 1

Since the synthesis of 2-piperidones is of interest because of their use as intermediates in the production of biologically active materials, we have extended the synthetic route to some 2-piperidones from α-amino acids similarly applying the Dieckmann condensation and have also investigated spectral properties of 2-piperidones (IX and X).

Readily available alanine and 3-phenylalanine were adopted as starting materials in the racemic form of their methyl esters (V). On treatment with methyl 3-chloroformylpropionate in the presence of potassium carbonate, the methyl esters (Va and Vb) gave the corresponding dimethyl esters (VIa and VIb) in 19 and 81% yields, respectively. The unsatisfactory yield of the former may be due to its facile water-solubility.

On the other hand the methyl esters (Va and Vb) were condensed with benzaldehyde, followed by catalytic hydrogenation over platinum oxide in methanol to give the N-benzyl esters (VIIa and VIIb) in good yields. Treatment of VIIa and VIIb with methyl 3-chloroformylpropionate afforded the dimethyl esters (VIIIa and VIIIb) in 91 and 83% yields.

1) Part VI: N. Takamura, S. Terashima, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **16**, 2059 (1968).
2) Location: *Hongo, Tokyo.*
3) T. Shioiri, and S. Yamada, *Tetrahedron Letters*, **1967**, 351; *idem*, *Tetrahedron*, **24**, 4159, 4177 (1968).

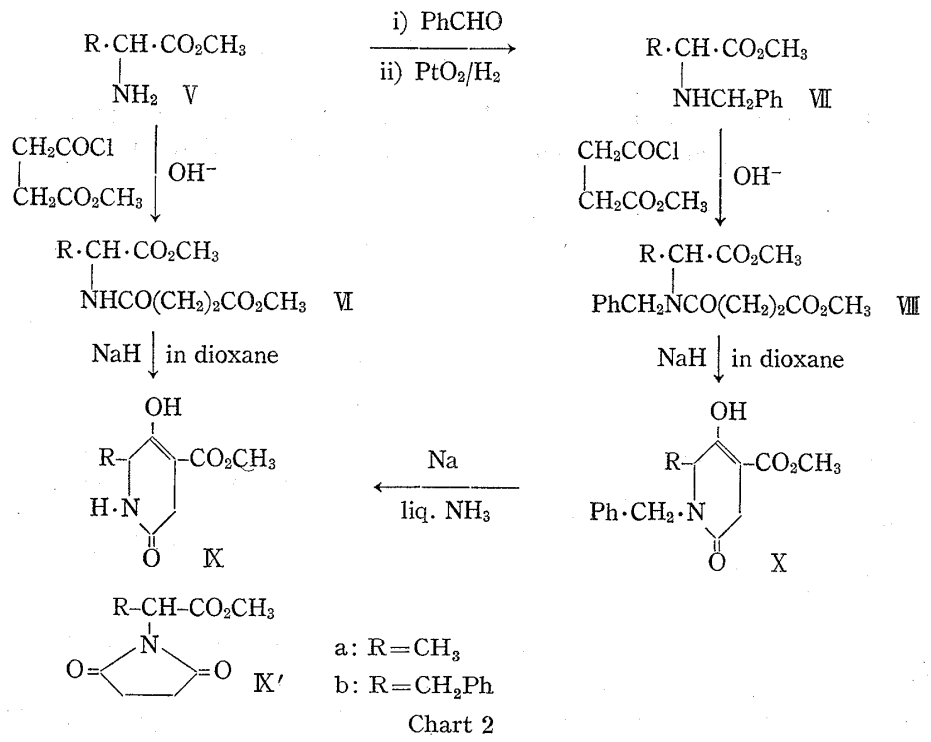


Chart 2

We have already disclosed[3] a combination of sodium hydride and dioxane to be the most effective reaction condition in the Dieckmann condensation[4] of some N-succinoylamino acid dimethyl esters, such as II. The dimethyl esters (VI and VIII) were, respectively, subjected to the Dieckmann condensation under the same base–solvent combination as shown in Table I. The structures of the respective, resultant 2-piperidones (IX and X) were supported by microanalytical and spectral data, the latter of which were fully discussed later in this paper, in addition to an intense coloration (reddish–purple) obtained with ferric chloride reagent.[5]

Table I. Dieckmann Condensation of Dimethyl Esters (VI and VIII)

Starting materials	NaH mole	Solvent	Bath temp.	Reaction time hr	Yields of IX or X
VIa	2	dioxane	105°	4	0.5%
VIIIa	1	dioxane	105°	4	18
	2	dioxane	105°	5.5	82
VIb	0.5	dioxane	105°	5	18
	1	dioxane	105°	5	36
	2	dioxane	105°	5	30
VIIIb	0.5	dioxane	105°	5	6
	1	dioxane	105°	5	52
	2	dioxane	105°	5	60

The cyclization of the N-unsubstituted esters (VI) to IX resulted in rather unsatisfactory yields, which may be caused by a competitive formation of the imide (IX').[3,6] Because of no imide formation, the corresponding N-benzyl derivatives (VIII) gave the expected products (X) in moderate or good yield when two equivalents of sodium hydride were used. Half equivalents of sodium hydride gave poor results. In consequence, the necessary quantity of sodium hydride in the cyclization of some N-succinoylamino acid dimethyl esters is one or two equivalents, preferably the latter.

4) For an extensive review, see J.P. Schaefer and J.J. Bloomfield, "Organic Reactions," Vol. 15, John Wiley & Sons, Inc., New York, 1967, p. 1.

The N-benzyl piperidones (Xa and Xb) were subjected to debenzylation in the presence of sodium and liquid ammonia[3,7] to give the N-unsubstituted ones (IXa and IXb) in moderate yields.

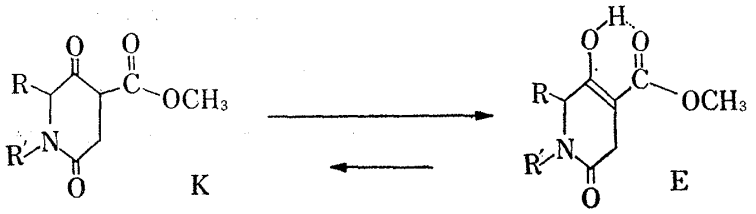
Spectral Properties

In general the infrared (IR) spectra of enolizable β-keto esters exhibit four bands in the double bond stretching region[5]: a pair at a higher frequency (1700 cm^{-1} region) associated with the keto tautomer and at a lower frequency pair (1600 cm^{-1} region) due to the chelated enol. The relative intensities of these two sets of bands vary with the enol content.

As shown in Table II, the IR spectra of the piperidones (IX and X) both in the solid state (KBr discs) and in solution (chloroform) show broad peaks of strong intensity in the 1680—1660 cm^{-1} region, which were assigned to the chelated, conjugated ester C=O stretching mode. The overlapping of the carbonyl absorption of enolic esters and lactams is found in the spectra of IXa and IXb (both in the solid state and in solution) and Xb (in the solid state). But the spectra of Xa (both in the solid state and in solution) and Xb (in solution) show two carbonyl bands: the enol esters in the higher frequency and the lactams in the lower frequency. The conjugated C=C stretching band in this series of compounds is not clearly assignable owing to its weakness and masking by the high intensity carbonyl band. Transparency in the 1700 cm^{-1} region strongly suggests high contents of the chelated enolic tautomers (E). This shows reasonably good agreement with the IR spectra of some β-keto esters (XI—XVI) in our previous paper.[3] The lower frequencies of enol ester carbonyl absorptions in the N-unsubstituted series (IX) than those in the N-benzyl ones (X) in solution suggest a stronger hydrogen bond in the former.

In accord with previous work[5] no bands attributable to free or chelated hydroxyl group were detected in any of the β-keto esters in this series.

Table II. IR and UV Spectra of β-Keto Esters (IX and X)



Compd.	R	R′	IR cm^{-1} in KBr	IR cm^{-1} in $CHCl_3$[a]	UV mμ (ε×10^{-3}) in 90% aq. EtOH	
IXa	CH_3	H	1663	1669	250	(8.15)
IXb	$PhCH_2$	H	1660	1668	251	(8.41)
Xa	CH_3	$PhCH_2$	1681, 1638	1683, 1645	250	(7.93)
Xb	$PhCH_2$	$PhCH_2$	1655	1682, 1643	252	(7.99)

a) Each solution was 0.03 mole / liter and was examined in 0.1 mm cells.

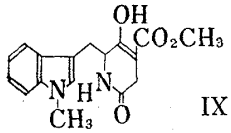
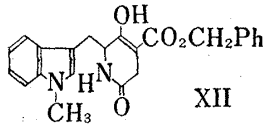
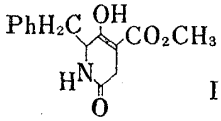
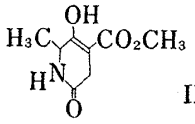
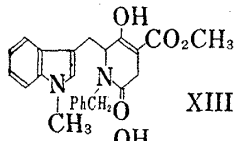
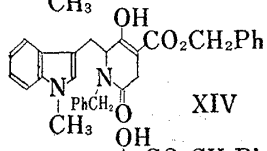
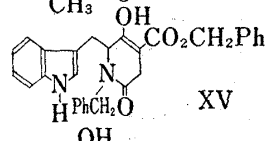
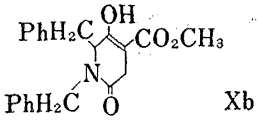
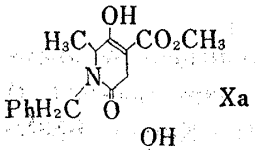
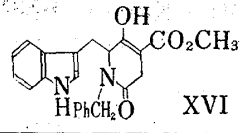
The ultraviolet (UV) spectra measured in 90% aqueous ethanol also confirmed the above conclusion. The indole derivatives (XI—XVI) in our previous paper[3] show maxima at about 258 mμ (ε 9000) in addition to the usual indolic absorptions at about 220 mμ (ε 40000) and 280—285 mμ (ε 6000). The 258 mμ band is largely attributable to the K-band of the

5) S.J. Rhoads, J.C. Gilbert, A.W. Decora, T.R. Garland, R.J. Spangler, and M.J. Urbigkit, *Tetrahedron*, **19**, 1625 (1963), and references therein.
6) H. Werbin and P.E. Spoerri, *J. Am. Chem. Soc.*, **69**, 1681 (1947).
7) S. Sugasawa and T. Fujii, *Chem. Pharm. Bull.* (Tokyo), **6**, 587 (1958).

chelated enolic esters, which is shifted to a slightly longer wave length by the underlying indole chromophore than those of the present piperidone derivatives.

The piperidones (IX and X) show maxima with high intensity (ε 8000) at 250 mμ. The difference in ε between the indole derivatives (XI—XVI) and the piperidones (IX and X) arises from the indole chromophore of the former. The low intensity R-band of the keto form, which is expected to lie in the 280—300 mμ,[5] is completely masked by the high intensity K-band of the chelated enol form. The slightly higher ε of IX than that of X suggests a stronger hydrogen bond for IX.

Table III. NMR Spectra of β-Keto Esters (IX—XVI) in $CDCl_3$ Solutions[a]

Compounds	Enolic OH	NCH_2Ph Center of the AB quartet	NCH_2Ph the difference of two doublets	J cps	CO_2CH_3 or CO_2CH_2Ph	C_6–H of piperidone	Aromatic H	Ind. α-H	Ind.-NH or ind.-NCH_3
 IX	−2.11	—	—	—	6.24	5.75	2.77	3.08	6.24
 XII	−2.10	—	—	—	4.83	5.77	2.69	3.10	6.30
 IXb	−2.07	—	—	—	6.21	5.65	2.76	—	—
 IXa	−2.03	—	—	—	6.17	5.80	—	—	—
 XIII	−1.88	5.26	1.69	15	6.27[b]	5.88	2.74	3.26	6.42[b]
 XIV	−1.86	5.25	1.71	14	4.98	5.86	2.73	3.26	6.30
 XV	−1.84	5.20	1.69	15	5.00	5.83	2.72	3.18	1.13
 Xb	−1.82	5.27	1.76	14	6.30	5.92	2.85	—	—
 Xa	−1.78	5.30	1.43	16	6.18	6.04	2.72	—	—
 XVI	−1.76	5.23	1.68	15	6.46	5.87	2.76	3.21	1.48

a) Each compound was measured as a 0.3 mole/liter solution at 25°, relative to TMS as an internal standard.
b) The assignment is tentative.

The nuclear magnetic resonance (NMR) technique is often a powerful tool to clarify the keto–enol equilibrium.[8] The strong deshielding of internal hydrogen bonding in enolic chelates is well recognized and it is generally accepted that the magnitude of the displacement of the OH signal to the lower field is related to the strength of the hydrogen bond.[8] Thus, NMR studies have been made of the 2-piperidones including XI—XVI as prepared in our previous paper.[3]

The 2-piperidones (IX—XVI) in Table III can be grouped in two classes according to the chemical shift of enolic protons. This classification also corresponds to that based on the presence or absence of N-benzylated group.

Enolic protons in the N-unsubstituted piperidones resonate at τ −2.11——2.03 as sharp 1 H singlets, while the signals of corresponding protons of the N-benzyl derivatives are found slightly upfield from these, at τ −1.88——1.76. This suggests that these β-keto esters mainly exist in the chelated enolic form and that the hydrogen bond of the N-unsubstituted piperidones is stronger than that of the N-benzyl derivatives. This result coincides with the conclusion obtained from the IR and UV spectra.

The geminal methylene protons of the N-benzyl group in the N-benzyl series are a point of further interest. Without exception the N-benzyl piperidones reveal the methylene signals of the N-benzyl group as an AB system with J=15 cps. This magnetic nonequivalence arises from the restricted rotation around the methylene C–N bond of the N-benzyl group. A similar phenomenon has been observed in a number of N-benzyl lactams.[3,9]

Protons of the ester groups exhibit sharp singlets for the methyl esters at τ 6.17—6.46 and for the benzyl esters at τ 4.83—5.00.

The NMR spectra of all compounds show multiplets for the C–6 protons with centers at about τ 5.8 in addition to multiplets for aromatic protons centered at about τ 2.8.

Each indole derivative has an 1H peak at about τ 3.1 which is characteristic of an indolic α-proton.[10] In contrast to the sharp singlet for the ind.-N methyl series (XI—XIV), the α-proton of ind.-N unsubstituted ones shows doublets (J=2.4 cps) which are split by the proton attached to ind.-N. Ind.-N methyl peaks and ind.-N hydrogen are, respectively, observed at about τ 6.3 and at about τ 1.3.

These NMR spectra in company with the IR and UV spectra support the assigned structure of all piperidone derivatives bearing the β-keto ester functions which primarily exist in chelated enolic tautomers.

Experimental[11]

N-Benzylalanine Methyl Ester (VIIa)——N-Benzylidenealanine methyl ester (42 g, 0.22 mole), prepared by the method of Yoshida,[12] in methanol (250 ml) was hydrogenated over PtO_2 (0.45 g) at room temperature and atmospheric pressure; the reaction ceased after 5 hr (H_2 uptake in slight excess of one molar equivalent). Filtration and evaporation of the filtrate gave a slightly yellow viscous oil, which was distilled at 142—145° (18 mmHg) (lit.[13] bp 130—132° (11 mmHg)) to give colorless VIIa (34.5 g, 81.2%).

8) S.J. Rhoads, *J. Org. Chem.*, **31**, 171 (1966), thoroughly investigated the tautomeric behavior of some enolizable cyclic β-keto esters by means of the NMR. See also references therein.

9) A.H. Lewin, J. Lipowitz, and T. Cohen, *Tetrahedron Letters*, **1965**, 1241; P.L. Southwick, J.A. Fitzgerald, and G.E. Milliman, *ibid.*, **1965**, 1247; K.D. Barrow and T.M. Spotswood, *ibid.*, **1965**, 3325.

10) L.A. Cohen, J.W. Daly, H. Kny, and B. Witkop, *J. Am. Chem. Soc.*, **82**, 2184 (1960); R.V. Jardine, and R.K. Brown, *Canad. J. Chem.*, **41**, 2067 (1963); M.G. Reinecke, H.W. Johnson, Jr. and J.F. Sebastian, *Chem. & Ind.*, **1964**, 151; Part II in this Series, K. Ishizumi, T. Shioiri, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **15**, 863 (1967).

11) All melting points and boiling points are uncorrected. IR spectra were measured on a Jasco-DS-402G spectrophotometer, UV spectra on a Cary Model 11 spectrophotometer, and NMR spectra on a Jeolco 3H-60 instrument at 60 Mc. Solvents used for extraction were dried over anhyd. sodium sulfate after extraction, and removed under reduced pressure. Experiments on compounds of the alanine series are described as typical examples.

12) N. Yoshida, *Yakugaku Zasshi*, **82**, 841 (1962).

N-Benzyl-3-phenylalanine Methyl Ester (VIIb)——N-Benzylidene-3-phenylalanine methyl ester[12] was similarly hydrogenated to the N-benzyl derivative (VIIb) as a colorless oil in 75% yield, bp 165° (0.55 mmHg) (lit.[14] bp 137—141° (0.3 mmHg)).

N-(3-Methoxycarbonylpropionyl)alanine Methyl Ester (VIa)——Methyl 3-chloroformylpropionate[15] (39 g, 0.26 mole) was added dropwise ot a stirring mixture of alanine methyl ester[16] (20.6 g, 0.20 mole), acetone (300 ml) and dry powdered potassium carbonate (83 g, 0.6 mole) at 0 — −5° (internal temperature) during 0.5 hr. The reaction mixture was allowed to warm to room temperature and stirred for 2 hr. Inorganic materials were filtered and wahed with acetone. Evaporation of the combined filtrates gave an oily residue which was dissolved in benzene (200 ml), and the solution was successively washed with water, aq. potassium carbonate, 10% aq. hydrochloric acid, water and saturated aq. sodium chloride. Drying and evaporation left a red viscous oil which was distilled at 180—185° (12 mmHg) to give VIa (8.4 g, 19%) which was crystallized by chilling with a dryice–acetone bath, mp 52°. *Anal.* Calcd. for $C_9H_{15}O_5N$; C, 49.76; H, 6.96; N, 6.45. Found: C, 49.60; H, 7.06; N, 6.62. IR ν_{max}^{KBr} cm^{-1}: 3320 (NH), 1745 (ester), 1655 (amide I), 1543 (amide II).

N-(3-Methoxycarbonylpropionyl)-3-phenylalanine Methyl Ester (VIb)——Methyl 3-chloroformylpropionate[15] (88 g, 0.58 mole) was added dropwise to a stirring mixture of 3-phenylalanine methyl ester[17] (Vb), (80 g, 0.45 mole) benzene (300 ml) and 17 w/v% aq. potassium carbonate (475 ml, 0.58 mole) at 5—10° (internal temperature) during 1 hr. The reaction mixture was allowed to warm to room temperature and stirred for 1.5 hr. The benzene layer was washed succesively with 10% aq. sodium carbonate, water, 10% aq. hydrochloric acid, water and saturated aq. sodium chloride. Drying and evaporation of the solvent gave colorless crystals (108 g, 81%). For analysis a sample was recrystallized from benzene–*n*-hexane (1:2) to give colorless needles, mp 73°. *Anal.* Calcd. for $C_{15}H_{19}O_5N$: C, 61.42; H, 6.53; N, 4.78. Found: C, 61.28; H, 6.50; N, 5.01. IR ν_{max}^{KBr} cm^{-1}: 3322 (NH), 1745, 1731 (ester), 1643 (amide I), 1535 (amidd II), 740, 700 (benzene).

N-Benzyl-N-(3-methoxycarbonylpropionyl)alanine Methyl Ester (VIIIa)——The methyl ester (VIIa) was treated as in the case of Va. Yield 91%, bp 195—200° (0.3 mmHg). IR ν_{max}^{Cap} cm^{-1}: 1755 (ester), 1670 (amide), 741, 702, 686 (benzene).

N-Benzyl-N-(3-methoxycarbonylpropionyl)-3-phenylalanine Methyl Ester (VIIIb)——The methyl ester (VIIb) was treated as in the case of Vb to give a yellow viscous oil of VIIIb in 83% yield. IR ν_{max}^{Cap} cm^{-1}: 1750 (ester), 1670 (amide), 756, 740, 704 (benzene).

Dieckmann Condensation of Dimethyl Esters (VI and VIII)——See Table I for the various conditions employed. Typical procedure was described in the case of Xa.

Methyl 1-Benzyl-5-hydroxy-6-methyl-2-oxopiperid-4-en-4-carboxylate (Xa): A suspension of sodium hydride (obtained from 12.5 g (0.26 mole) of a 50% oil dispersion by washing with anhyd. benzene and dioxane in anhyd. dioxane (100 ml) was added to a solution of the dimethyl ester (VIIIa) (37.3 g, 0.12 mole) in anhyd. dioxane (150 ml) and stirred under N_2. The mixture was heated at 100—110° (bath temperature) for 5.5 hr. After removal of the solvent the residue was dissolved in a minimum amount of water. The aq. layer was washed with benzene, acidified with conc. hydrochloric acid under ice–cooling, and extracted with ethyl acetate. The organic layer was washed successively with water, saturated aq. sodium bicarbonate, water, and saturated aq. sodium chloride. Dyring and evaporation gave the solid residue (27 g, 82%).

Table IV. Methyl 5-Hydroxy-6-alkyl-2-oxopiperid-4-en-4-carboxylates (IX and X)

Compd.	mp	Recryst. Solvents	Appearance	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
IXa	147.5—148.5°	methanol	slightly yellow needles	$C_8H_{11}O_4N$	51.88	5.99	7.56	51.70	5.97	7.85
IXb	150—151.5°	benzene	colorless needles	$C_{14}H_{15}O_4N$	64.36	5.79	5.36	64.27	5.86	5.37
Xa	80—81°	acetone	colorless prisms	$C_{15}H_{17}O_4N$	65.44	6.22	5.09	65.49	5.87	5.33
Xb	111—112°	benzene –*n*-hexane	colorless prisms	$C_{21}H_{21}O_4N$	71.78	6.02	3.99	72.01	5.97	3.72

13) A. Cohen, J.W. Haworth, and E.G. Hughes, *J. Chem. Soc.*, **1952**, 4374.
14) A. Cohen and J.A. Silk, *J. Chem. Soc.*, **1952**, 4386.
15) J. Cason, "Organic Syntheses," Coll. Vol. III, ed. by E.C. Horning, John Wiley & Sons, Inc., New York, 1955, p. 169.
16) H. Zahn and H. Schussler, *Ann.*, **641**, 176 (1961).
17) Th. Curtius and E. Muller, *Ber.*, **37**, 1267 (1904).

Debenzylation of N-Benzylpiperidones (X)——Methyl 5-Hydroxy-6-methyl-2-oxopiperid-4-en-4-carboxy late (IXa): Metallic sodium (0.65 g, 0.028 atom) was added, with stirring, in small pieces to N-benzyl-piperidone (Xa) (2.86 g, 0.01 mole) in liquid ammonia (80 ml) over a 10 min period. After evaporation of the ammonia, the white residue was dissolved in water (30 ml). The aq. layer was washed with ether, neutralized with conc. hydrochloric acid to pH 8.5, andextracted with benzene–ethyl acetate (1:5). The organic layer was washed with saturated aq. sodium chloride, dried and evaporated to the yellow solid (0.80 g, 42%), which was identified with the product (IXa) through VIa by IR comparison.

Methyl 5-Hydroxy-6-benzyl-2-oxopiperid-4-en-4-carboxylate (IXb): The debenzylation of Xb was carried out as above to give IXb in 67% yield.

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