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A NEW SYNTHESIS OF PYRIDONES AND UNSATURATED LACTAMS[1]

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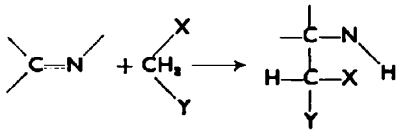
Abstract—The condensation of diethyl glutaconate (I) with imines leads to unsaturated ester lactams which, in some cases, can be isomerized to pyridones. Thus I with N-benzylidenemethylamine yields ester lactam (IV) and I with benzalaniline yields IVa. Saponification of IV and IVa produces the isomerized pyridone carboxylic acids VI and VIa respectively which can be decarboxylated to pyridones (IX and IXa). The sequence involving saponification of IV followed by Fischer esterification gives the pyridone VIII, isomeric with IV.

Alternatively, the ester lactam (IV) can be converted to the corresponding thiolactam (V) with P_2S_5, or to the pyridone (XII) via bromination followed by treatment with ethanolic KOH. Both IV and IVa can be reduced catalytically to the piperidones X and Xa. Condensation of I with diphenylketimine gives the ester lactam (XIV) which does not isomerize under saponifying conditions, but leads to the acid (XV) and benzophenone.

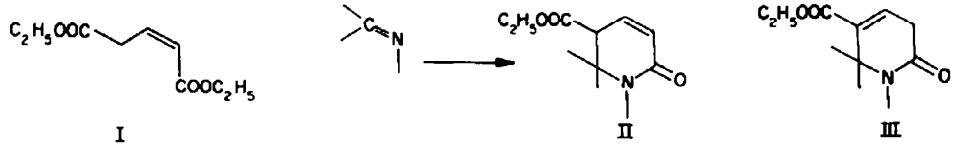
THE addition of compounds possessing active methylenes to Schiff bases has been extensively investigated. The general reaction, which is formally analogous to an aldol condensation, can be represented by Eq. (i) in which either or both X and Y represent electron withdrawing groups:



(i)

Compounds with active methylene groups that have been used are esters, acids, acid salts, amides, nitro compounds, indoles and anils (self-condensation), and also aldehydes and ketones[2]; the addition to ketones having been very recently reconsidered by Blatt and Gross.[3]

In an attempt to extend the usefulness of this condensation, we have investigated the reaction between diethyl glutaconate (I) and three disubstituted imines. Our original belief was that such a condensation, if successful, would be immediately followed by cyclization with the formation of such unsaturated lactams as II or III:



I II III

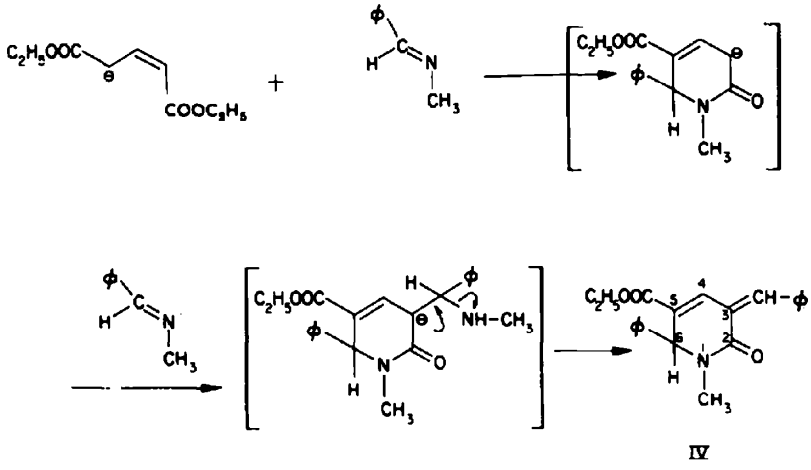
[1] This paper can be considered the third in the series entitled Unsaturated Lactams. For the previous paper see M. Shamma and P. D. Rosenstock, *J. Org. Chem.* **26**, 2586 (1961).

[2] For recent reviews on the reactions of imines, see W. F. Smith, *Organic Chemical Bulletin* **35**, 1 (1963); and Robert W. Layer, *Chem. Rev.* **63**, 489 (1963)

[3] A. H. Blatt and N. Cross, *J. Org. Chem.* **29**, 3306 (1964).

Diethyl glutaconate was therefore refluxed with N-benzylidenemethylamine in xylene for ten days. The pale yellow crystals obtained in high yield did not, however, analyze for the anticipated $C_{15}H_{17}NO_3$ resulting from the condensation of one mole of imine with one mole of diester, but rather for $C_{22}H_{21}O_3N$. The IR spectrum of the product showed absorption at 5·85 μ (α,β-unsaturated ester) and at 6·03 μ (lactam). The NMR spectrum, beside indicating that only one carbethoxy group was present, showed one N-methyl group at 2·88 ppm, and three hydrogens each as a singlet at 5·30, 7·72 and 8·00 ppm.

These data could be interpreted on the basis of structure IV which results from the condensation of a second mole of imine with the anion of the expected but unisolated lactam III, followed by elimination of methyl amine:

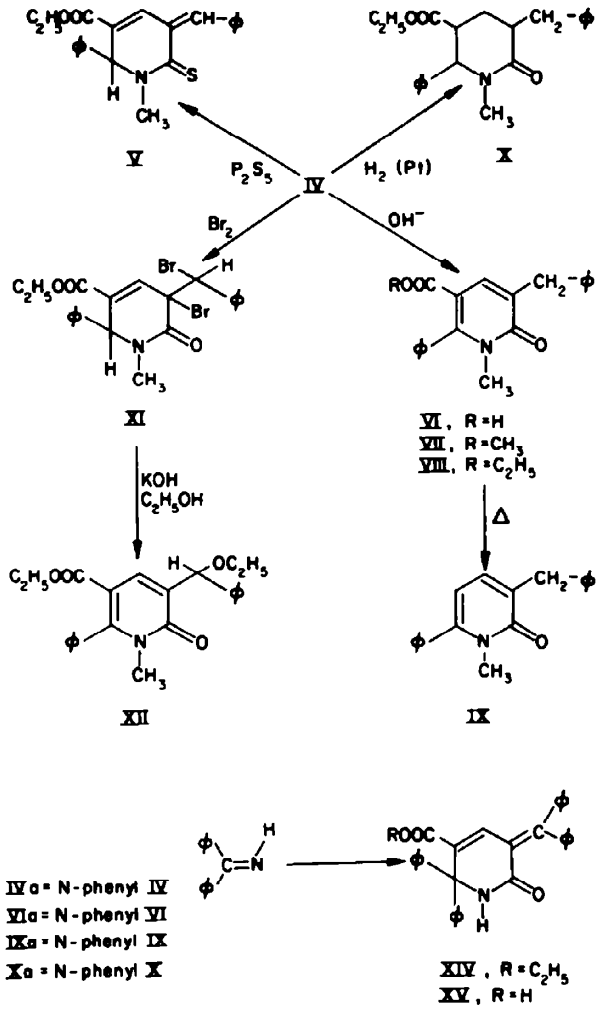


IV

The C-6 hydrogen of IV being benzylic, allylic, and also adjacent to a nitrogen atom would be expected to absorb as low as 5·30 ppm. The vinylic protons at C-4 and on the C-3 benzal function are also highly deshielded and consonant with chemical shifts of 7·72 and 8·00 ppm. It was found possible to assign the peak at 8·00 ppm to the C-3 benzal hydrogen through the expedient of preparing the corresponding thiolactam (V) obtained by refluxing the ester lactam (IV) in phosphorus pentasulphide. The NMR spectrum of the ester thiolactam (V) was close to that of IV with the exception that the singlet absorption at 8·00 ppm had now shifted to 8·67 ppm. Since in the ester lactam (IV) the C-3 benzal hydrogen is both in conjugation with the lactam function and in the immediate vicinity of the oxygen atom of that function, this is the hydrogen that would be expected to be the most affected by a change from a lactam to a thiolactam function.[4] The alternate singlet absorption at 7·72 ppm in compound IV can, therefore, be assigned to the vinylic hydrogen at C-4.

It would be expected that a structure such as IV should be easily isomerized to a pyridone nucleus, and this was indeed the case when we attempted its saponification. A crystalline acid was obtained in good yield which from spectral evidence was the rearranged pyridone carboxylic acid (VI). The UV spectrum was substantially different from that of the ester lactam IV (see Table), while the IR spectrum showed absorption

[4] It can be stated on steric grounds that the C-3 benzal hydrogen in IV in probably *syn* to the lactam carbonyl while the phenyl group is *anti*; and the same situation must prevail in the thiolactam V.



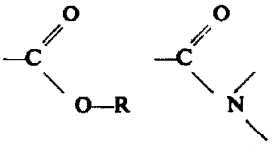
between 3·03 and 3·45 μ (OH hydrogen bonded and CH), at 5·86 μ (conj. COOH), and 6·06 μ (pyridone carbonyl). This acid was too insoluble in deuteriochloroform to allow an NMR spectrum, but esterification with either diazomethane or with methanol–HCl gave a colourless crystalline methyl ester (VII) with the following NMR spectrum: N–CH_3 at 3·25 ppm, $COOCH_3$ at 3·50 ppm, C-4 H at 7·85 ppm, and C-3 methylene at 3·97 ppm; all these peaks being singlets. Alternatively, esterification with ethanol–HCl gave the corresponding ethyl ester (VIII) which was clearly different from the initial ester lactam IV (see Table).

To further ascertain the structures here under consideration, the acid VI was decarboxylated to 1-methyl-3-benzyl-6-phenyl-2-pyridone (IX). The most salient point about the NMR spectrum of this new pyridone is the presence of two doublets, each representing one proton, at 6·90 and 5·83 ppm (J = 7·5 c/s), corresponding to the C-4 and C-5 hydrogens respectively. This order in the assignment of NMR peak can be made safely since it has been shown that the C-4 proton of a pyridone will

absorb at lower field than the C-5 proton.[5] Additionally, the N–CH_3 peak showed up relatively downfield at 3·31 ppm rather than further upfield as is the case with the ester lactam (IV).

The unsaturated ester lactam (IV) could also easily be hydrogenated with Adams catalyst to the tetrahydro derivative (X). When an attempt was made to brominate the unsaturated ester lactam (IV) a clear yellow oil was obtained whose IR spectrum

TABLE OF ULTRAVIOLET AND INFRARED DATA

Compounds	λ_{max}^{EtOH}	(log e)	λ_{min}^{EtOH}	(log e)	Carbonyl stretching vibrations	
						
IV	322	(4·39)	270	(3·72)	5·85 μ	6·03 μ
IVa	323	(4·41)	271	(3·75)	5·85	6·02
V	320	(4·32)	240	(3·87)	5·88	—
VI	267	(4·03)	241	(3·69)	5·86	6·06
	307	(3·94)	287	(3·83)		
VIa	266	(4·05)	242	(3·83)	5·87	6·05
	311	(3·96)	286	(3·79)		
VIII	270	(4·15)	242	(3·80)	5·91	6·12
	306	(4·03)	288	(3·96)		
IX	316	(4·09)	268	(3·38)	—	6·10
IXa	322	(4·05)	273	(3·43)	—	6·06
X		—		—	5·78	6·17
Xa		—		—	5·79	6·12
XII	267	(4·07)	244	(3·82)	5·89	6·10
	310	(4·00)	287	(3·83)		
XIV	340	(4·20)	280	(3·94)	5·86	6·02
	sh. 248	(4·13)				
XV		—		—	5·97	6·04

showed a conjugated ester peak at 5·86 μ and a lactam carbonyl at 6·08 μ.[6] This oil was too unstable for elemental analysis. It was, therefore, immediately treated at near 0° with a 5% KOH in ethanol solution. Purification of the product by column chromatography over alumina gave a neutral clear oil which crystallized to a colourless solid, $C_{24}H_{25}O_4N$ (XII). This material had an UV spectrum almost identical with that of the pyridone ester VIII (see Table). The IR spectrum showed an unsaturated ester peak at 5·89 μ and a pyridone carbonyl at 6·10 μ. The NMR spectrum showed the presence of two different ethoxy groups (two triplets and two quartets), while a peak corresponding to a benzylic proton adjacent to an ether oxygen appeared downfield at 5·47 ppm as a singlet. Additionally, the N–CH_3 peak appeared at 3·06 ppm.

The unstable brominated intermediate can, therefore, tentatively be formulated as XI, resulting from 1,2 addition of bromine across the exocyclic double bond. This dibromide on treatment with base must then have undergone elimination of HBr

[5] J. A. Elvidge and L. M. Jackman, *J. Chem. Soc.* 859 (1961).
[6] A. J. Verbiscar and K. N. Campbell, *J. Org. Chem.* **29**, 3306 (1964).

together with substitution at the benzylic position rather than saponification of the ester function.

In an analogous series of transformations, diethyl glutaconate (I) was condensed with benzalaniline to the N-phenyllactam ester (IVa). This product underwent saponification accompanied by rearrangement to the carboxylic acid (VIa). In turn, the carboxylic acid (VIa) could be decarboxylated to the pyridone (IXa). The N-phenyllactam ester (IVa) could also be reduced catalytically to the piperidone (IXa).

The condensation of diethyl glutaconate with the symmetrically substituted diphenyl ketimine (XIII) in xylene as solvent was also investigated, and gave the crystalline ester lactam (XIV). Saponification of this compound gave the corresponding carboxylic acid lactam (XV) together with substantial amounts of benzophenone. The formation of benzophenone is a reflexion of the atavistic tendencies of the ester lactam (XIV) since this heterocycle does not have the alternative of isomerizing to a stable pyridone structure as was the case with compounds IV and IVa.

We are presently continuing our studies on the condensation of imines with unsaturated esters possessing active methylenes.

EXPERIMENTAL[7]

1-Methyl-2-oxo-3-benzal-5-carbethoxy-6-phenyl-Δ^4-piperideine (IV)

A mixture of 9·6 g (0·08 mole) N-benzylidenemethylamine[8] and 5·1 g (0·027 mole) diethyl glutaconate[9] was dissolved in xylene and refluxed for 10 days under a N_2 atm. in a round-bottom flask equipped with a condenser. The xylene was then evaporated *in vacuo*, and the residue crystallized on standing. The crystals were washed with ice cold EtOH, and then recrystallized from hot EtOH. The yield was 8·08 g (85%) pale yellow crystals, m.p. 123·5–124·5°. NMR absorption at 2·88 ppm N–CH_3, at 5·30 ppm C-6H, at 7·72 ppm C-4H, and at 8·00 ppm C-3 benzal vinylic H. (Found: C, 76·35; H, 6·24. Calc. for $C_{28}H_{31}O_3N$: C, 76·06; H, 6·09%.)

1,6-Diphenyl-2-oxo-3-benzal-5-carbethoxy-Δ^4-piperideine (IVa)

A mixture of 10 g (0·055 mole) benzalaniline[10] and 10·2 g (0·055 mole) diethyl glutaconate was heated on a steam bath for 1 week. At the end of this time the solution was cooled, and a little cold EtOH added, whereupon the oil crystallized. Three recrystallizations from EtOH gave 4·77 g (42%) light yellow crystals, m.p. 185–185·5°. NMR absorption at 5·68 ppm C-6H, at 7·83 ppm C-4H, and at 8·07 ppm C-3 benzal vinylic H. (Found: C, 78·90; H, 5·73; N, 3·60. Calc. for $C_{27}H_{23}O_3N$: C, 79·19; H, 5·66; N, 3·42%.)

1-Methyl-3-benzyl-6-phenyl-2-pyridone-5-carboxylic acid (VI)

One gram (2·9 mmoles) IV was dissolved in 50 ml 5% KOH in MeOH, and the solution refluxed for 1 hr on the steam bath. The reaction mixture was then cooled, and the MeOH evaporated. The residue was acidified in the cold with dil. HCl, and extracted with ether. The ether layer was separated and the solvent evaporated. The solid residue was washed with EtOH, and then recrystallized from hot EtOH. The colourless crystals thus obtained, 900 mg (97%), melted 293–294°. (Found: C, 75·41; H, 5·69. Calc. for $C_{20}H_{17}O_3N$: C, 75·22; H, 5·37%.)

[7] All NMR spectra were run in $CDCl_3$ solution with tetramethylsilane as an internal standard, using a Varian A-60 instrument. IR spectra were run in $CHCl_3$-solution using a Beckmann IR-5A spectrometer. All m.ps. are uncorrected. Elemental analyses are by Midwest Microlab, Inc., Indianapolis, Indiana.

[8] N. H. Cromwell, R. D. Babson and C. E. Harris, *J. Amer. Chem. Soc.* 65, 312 (1943).

[9] Purchased from Aldrich Chemical Company, Milwaukee, Wisconsin.

[10] L. A. Bigelow and H. Eatough, *Organic Syntheses* (Edited by H. Gilman and A. H. Blatt; 2nd edition) Coll. Vol. I; p. 80. 1961.

1,6-Diphenyl-3-benzyl-2-pyridone-5-carboxylic acid (VIa)

The saponification of IVa was carried out as in the case of IV. The yield of acid was 71%, m.p. 251–252° (dec). (Found: C, 78·48; H, 5·10; N, 3·81. Calc. for $C_{24}H_{19}O_3N$: C, 78·72; H, 5·02; N, 3·67%.)

1-Methyl-3-benzyl-6-phenyl-2-pyridone (IX)

A sample of VI weighing 0·23 g (0·72 mmole) was placed in a small Pyrex test tube which was immersed in a sand bath and then slowly heated under a stream of N_2. By the time 330° was reached, the material was brown and bubbling. A dark brown solid was obtained upon cooling, and this was chromatographed on Alcoa alumina (basic). Elution with MeOH–ether gave 169 mg (85%) of an oil which quickly solidified to a material, m.p. 71·5–72·5°. A suitable solvent for recrystallization could not be found, but an analytical sample was obtained by sublimation *in vacuo* with heating. NMR absorption at 3·31 ppm N–CH_3, at 3·81 ppm C-3 benzylic methylene, at 5·83 ppm C-5H, and at 6·90 ppm C-4H ($J_{4,5}$ = 7·5 c/s). (Found: C, 82·99; H, 6·36. Calc. for $C_{19}H_{17}ON$: C, 82·88; H, 6·22%.)

1,6-Diphenyl-3-benzyl-2-pyridone (IXa)

A sample consisting of 550 mg (1·4 mmoles) VIa was placed in a small Pyrex tube and heated as in the case above. The crude pyrolysate was taken up in $CHCl_3$ and washed with $NaHCO_3$ aq. The solution was then evaporated to an oil which crystallized upon the addition of a little EtOH and cooling. This material weighed 211 mg (44%), m.p. 141–142°. The analytical sample was prepared by sublimation *in vacuo*, with heating. NMR absorption at 3·82 ppm C-3 benzylic methylene. (Found: C, 85·46; H, 5·95. Calc. for $C_{24}H_{19}ON$: C, 85·43; H, 5·68%.)

1-Methyl-2-thio-3-benzal-5-carbethoxy-6-phenyl-Δ^4-piperideine (V)

One gram (2·9 mmoles) IV and 300 mg P_2S_5 was mixed with 50 ml xylene and heated for 30 min with vigorous stirring until the mixture almost came to a boil. The precipitate obtained upon filtration of the hot mixture was extracted with hot xylene, and the extract added to the original xylene solution. The residue obtained upon evaporation of the combined xylene solution crystallized upon cooling and the addition of a little cold EtOH. Orange crystals were thus obtained, weighing 500 mg (43%), m.p. 140–145°. Recrystallization from hot EtOH gave 450 mg (42%) orange crystals, m.p. 145–146°. NMR absorption at 3·50 ppm N–CH_3, at 5·60 ppm C-6H, at 7·77 ppm C-4H, and at 8·67 ppm C-3 benzal vinylic proton. (Found: C, 72·67; H, 6·02. Calc. for $C_{21}H_{21}O_2NS$: C, 72·71; H, 5·82%.)

Methyl 1-methyl-3-benzyl-6-phenyl-2-pyridone-5-carboxylate (VII)

Method I. Acid VI (500 mg, 1·6 mmoles) was dissolved in 25 ml absolute MeOH, and dry HCl gas bubbled into the solution for 20 min. The reaction mixture was then refluxed under anhydrous conditions for 12hr. The solvent was then evaporated, and the residue taken up in $CHCl_3$. After repeated extraction with $NaHCO_3$ aq, the $CHCl_3$ layer was dried over anhydrous K_2CO_3, filtered, and evaporated to dryness. The solid residue was recrystallized from EtOH to give white prisms, 400 mg (76%), m.p. 119–120°. NMR absorption at 3·25 ppm N–CH_3, at 3·97 ppm C-3 benzylic methylene, and at 7·85 ppm for C-4H. (Found: C, 75·73; H, 5·84. Calc. for $C_{21}H_{19}O_3N$: C, 75·65; H, 5·74%.)

Method II. Acid VI (319 mg, 1 mmole) was mixed with 20 ml MeOH (incomplete solution), and excess diazomethane in ether was distilled directly into the reaction flask which was maintained at about 0° in an ice bath. The reaction mixture was allowed to warm slowly to 15° with slight agitation, until all the acid was dissolved and evolution of N_2 had ceased. After the disappearance of the yellow colouration, the solvent was evaporated and the solid residue taken up in $CHCl_3$. Evaporation of the $CHCl_3$ after extraction with $NaHCO_3$ aq gave an oil which readily solidified. Recrystallization from EtOH gave white prisms, 250 mg (75%), m.p. 118·5–119·5°, with an IR spectrum identical with that of the product obtained by Method I above.

Ethyl 1-methyl-3-benzyl-6-phenyl-2-pyridone-5-carboxylate (VIII)

The procedure was identical with that followed in Method I above, except that absolute EtOH was used instead of MeOH. The product crystallized from EtOH as colourless prisms, m.p. 95–95·5° in

67% yield. NMR absorption at 5·25 ppm N–CH_3, at 3·97 ppm C-3 benzylic methylene, and at 7·80 ppm C-4H. (Found: C, 76·07; H, 6·34. Calc. for $C_{22}H_{21}O_3N$: C, 76·06; H, 6·09%.)

Ethyl 1-*methyl*-3-*benzyl*-6-*phenyl*-2-*piperidone*-5-*carboxylate* (X)

The ester lactam (IV; 1·06 g; 3·03 mmoles) was dissolved in 200 ml EtOH and 200 mg PtO_2 added. The hydrogenation was carried out in a Parr apparatus at 30 lbs/in² with shaking, for 30 hr. The catalyst was then filtered off, and the remaining oil crystallized on standing. The solid was recrystallized from 60% EtOH, yield 1·0 g (94%), m.p. 105–106°. (Found: C, 75·48; H, 7·19. Calc. for $C_{22}H_{25}O_3N$: C, 75·18; 7·17%.)

Ethyl 1,6-*diphenyl*-3-*benzyl*-2-*piperidone*-5-*carboxylate* (Xa)

Starting with IVa, the same procedure as in the catalytic hydrogenation described above was followed. The resulting oil from the reduction resisted crystallization, and was therefore chromatographed over neutral alumina using benzene–ether as the eluent. An oil was thus obtained which crystallized on standing, m.p. 50–51°. (Found: C, 78·58; H, 6·86. Calc. for $C_{27}H_{27}O_3N$: C, 78·42; H, 6·58%.)

Bromination of IV

The ester lactam (IV; 400 mg; 1·15 mmoles) was dissolved in 15 ml CCl_4 and 0·5 ml Br_2 added. The solution was refluxed for ½ hr, cooled to room temp and allowed to stand for 2 hr. Chloroform (20 ml) was then added, and the excess Br_2 destroyed by shaking with $Na_2S_2O_3$ aq. The solution was washed with water, dried over anhydrous $MgSO_4$, and evaporated to dryness *in vacuo*, the temp not exceeding 40°. The resulting brominated clear yellow oil (550 mg) was unstable.

Ethyl 1-*methyl*-3-*phenylethoxymethyl*-6-*phenyl*-2-*pyridone*-5-*carboxylate* (XII)

The above mentioned brominated oil (550 mg) was cooled to ice temp, and 20 ml ice cold 5% KOH in EtOH solution added dropwise with stirring. A cold 5% H_2SO_4 solution was then added dropwise until the mixture was very slightly acidic. The solution was subsequently evaporated to dryness *in vacuo*, and the residue extracted with $CHCl_3$. Evaporation gave a yellowish oil (442 mg) which after chromatography over basic alumina and elution with ether gave a clear oil which crystallized from 60% EtOH to long fine needles, m.p. 88·5–89·5°, 400 mg (90% yield based on 400 mg of starting ester lactam IV). NMR absorption at 3·06 ppm N–CH_3, and at 5·47 ppm for C-3 carbinyl H. Also two triplets centered at 0·85 and 1·20 ppm, and two quartets at 3·45 and 3·80 ppm, representing the two ethoxy groups present. (Found: C, 73·72; H, 6·72. Calc. for $C_{24}H_{25}O_4N$: C, 73·63; H, 6·44%.)

2-*Oxo*-3-*diphenylmethylene*-5-*carbethoxy*-6,6-*diphenyl*-Δ^4-*piperideine* (XIV)

A mixture of 15 g (0·08 mole) diethyl glutaconate and 35 g (0·19 mole) freshly prepared diphenylketimine[11] was dissolved in 125 ml dry benzene. Diphenylketimine hydrochloride, 1 g, was added as catalyst, and the mixture was refluxed under N_2 for 11 days. The xylene solvent was evaporated *in vacuo*, and the remaining dark oil taken up in benzene. The benzene solution was cooled in ice, and light petroleum ether slowly added. Some of the desired pale yellow product (1·58 g) precipitated out, m.p. 241–245°. More product was obtained by removing the solvent mixture *in vacuo*, dissolving the residue again in benzene, and shaking with dil. HCl to remove unreacted imine. Pale yellow crystals soon precipitated out of the benzene solution, so that the combined yield of product was 14·20 g (36%). The pale yellow analytical sample obtained by recrystallization from benzene–pet. ether, m.p. 251–252°. (Found: C, 81·52; H, 5·53. Calc. for $C_{33}H_{27}O_3N$: C, 81·62; H, 5·61%.)

2-*Oxo*-3-*diphenylmethylene*-6,6-*diphenyl*-Δ^4-*piperideine*-5-*carboxylic acid* (XV)

A sample of XIV (305 mg; 0·63 mmole) was added to 50 ml 2% KOH in EtOH solution, and the mixture refluxed for 2 hr. The solution was then evaporated to dryness, and 50 ml water added to the residue. The mixture was repeatedly extracted with ether, and subsequent evaporation of

[11] P. L. Pickard and T. L. Tolbert, *J. Org. Chem.* **26**, 4886 (1961).

the ether yielded a yellow oil (195 mg). Chromatography of this oil over basic alumina gave benzophenone (182 mg; 1 mmole) and a little starting XIV. Acidification of the basic aqueous layer with HCl was followed by repeated extraction with $CHCl_3$. The $CHCl_3$-extracts obtained after evaporation of the solvent gave an amorphous solid (68 mg; 21%) which readily crystallized from EtOH, m.p. 286–288°. (Found: C, 80·99; H, 5·30. Calc. for $C_{31}H_{33}O_3N$: C, 81·38; H, 5·07%.)

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