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STUDIES ON LACTAMS—VII[1]

A NEW SYNTHESIS OF β-AMINO-β-LACTAMS

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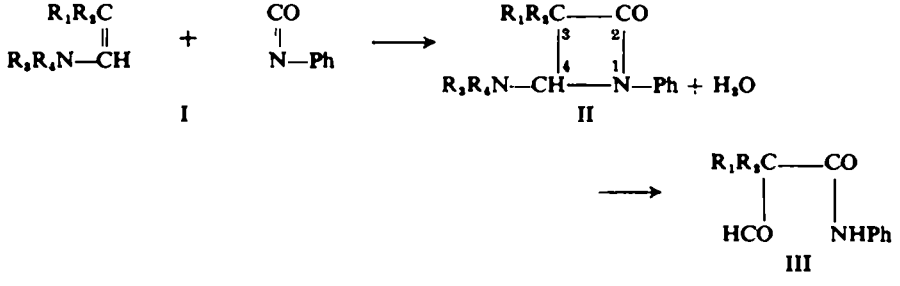
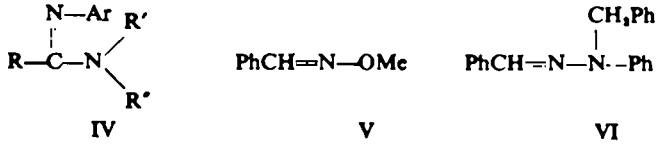
Abstract—A synthesis of β-amino-β-lactams has been achieved by the cyclo-addition of diphenylketene and N,N,N'-trisubstituted amidines. Since these β-lactams undergo facile decomposition in presence of a trace of moisture, their purification proved very difficult. However, it was possible to isolate four crystalline β-amino-β-lactams. The hydrolysis of 3,3-diphenyl-4-amino-2-azetidinones proceeds along a different path from that of 3,3-dialkyl-4-amino-2 azetidinones. A mechanism involving the formation of a carbanion on carbon 3 stabilized by two phenyl groups is suggested.

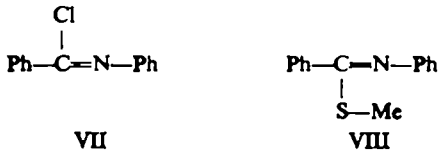
THE discovery that the antibiotics penicillin and cephalosporin C contain the α-amido-β-lactam unit has led to an interest in the synthesis of substituted amino-β-lactams. Two groups of workers[2,3] announced recently the same method for the synthesis of β-amino-β-lactams. The reaction[2,3] of phenyl isocyanate with β,β-disubstituted enamines (I) was shown to produce substituted 4-amino-2-azetidinones (II) which were unstable to moisture and readily decomposed to give α-formylacetanilide derivatives (III).



An examination of the β-amino-β-lactam structure reveals that it could possibly arise from the cycloaddition of a ketene and an amidine such as IV. The reaction of ketenes with several types of compounds containing the imino group, as for example, the oxime-ether V, the phenylhydrazone VI and the imido chloride VII, has been previously investigated in other laboratories. It was reported[4,5] that V, VI, and VII



[1] Part VI., A. K. Bose and B. Anjaneyulu, *Chem. and Ind.* 903 (1966).
[2] M. Perelman and S. A. Mizsak, *J. Amer. Chem. Soc.* **84**, 4988 (1962).
[3] G. Opitz and J. Koch, *Angew. Chem.* **75**, 167 (1963).
[4] H. Staudinger, *Die Ketene*. F. Enke, Stuttgart (1912).
[5] H. Staudinger, *Liebigs Ann.* **356**, 51 (1907).



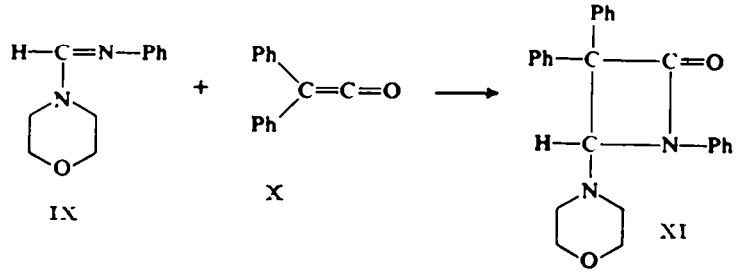
VII VIII

do not react with ketenes to form β-lactams. The imido thioester VIII, however, reacted with dimethylketene to give the corresponding β-lactam.[6] That the presence of sulfur substituent on the carbon of the imino group does not prevent β-lactam formation was further demonstrated by the synthesis of fused β-lactams from ketenes and thiazolidines.[7,8] The reaction of ketenes with amidines appears not to have been explored previously.

The standard method for the preparation of trisubstituted amidines involves the reaction of disubstituted amides with primary amines in presence of phosphorus oxychloride.[9] We found this method to be satisfactory. For the reaction with amidines, we chose diphenyketene since it is readily obtained and was found by Staudinger[4] to be one of the most reactive ketenes for the preparation of β-lactams.

Diphenylketene (X) prepared by dehydrohalogenation of diphenylacetyl chloride,[10] was added at room temperature to an ether solution of N,N-dimethyl-N'-phenyl-formamidine. The reaction product showed an absorption band at 5·67 μ which indicated the formation of the β-lactam but the oily product could not be purified. The attempted purification by column chromatography yielded a crystalline, colorless solid which was identified as diphenylacetanilide by comparison with an authentic sample.

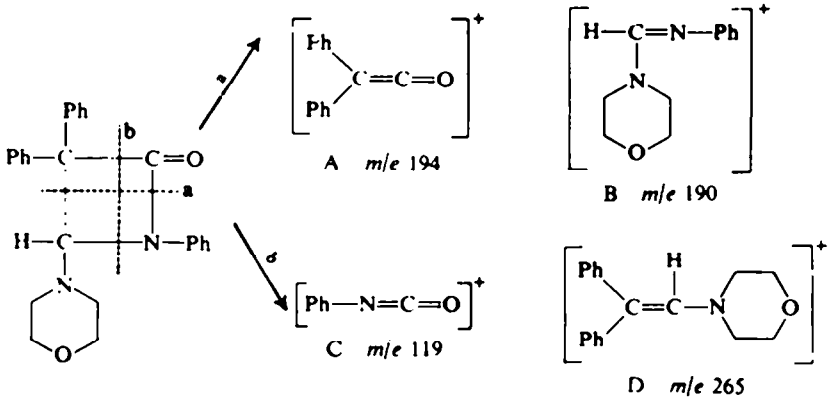
The reaction of diphenylketene (X) with 4-(N-phenylformimidoyl)-morpholine (IX) resulted in the formation of crystalline 1,3,3-triphenyl-4-morpholinoazetidinone (XI), m.p. 114–115°, which was obtained in about 45% yield; the infrared spectrum of XI showed absorption at 5·72 μ. The NMR spectrum of XI displayed signals at τ 2·24–2·94 corresponding to 15 aromatic protons; a singlet at τ 4·56 representing the hydrogen on carbon-4; a triplet centered at τ 6·63 corresponding to 4 protons on carbons adjacent to the oxygen, and a triplet at τ 7·39 corresponding to 4 protons



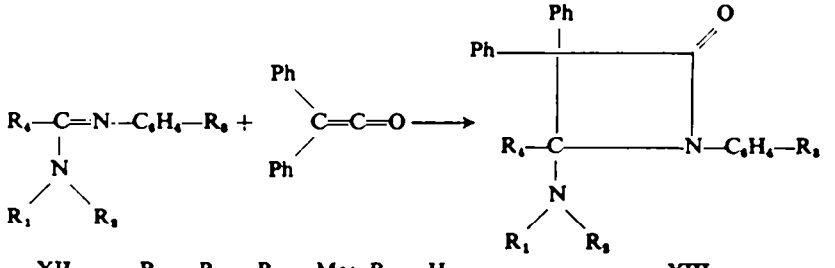
IX X XI

[6] R. H. Holley and A. D. Holley, *J. Amer. Chem. Soc.* 73, 3172 (1951).
[7] H. T. Clarke, J. R. Johnson and R. Robinson, *The Chemistry of Penicillin*. Princeton University Press (1949).
[8] J. C. Sheehan and E. J. Corey, *Organic Reactions* 9, 388 (1957).
[9] Houben-Weyl, *Methoden der Organischen Chemie* Band XI/2; p. 65. Georg Thieme Verlag, Stuttgart (1958); J. von Braunn, *Ber. Dtch. Chem. Ges.* 37, 2678 (1904).
[10] H. Staudinger, *Ber. Dtsch. Chem. Ges.* 44, 1619 (1911).

on carbons adjacent to the nitrogen in the morpholine moiety. The mass spectrum of XI does not exhibit a molecular ion peak but shows peaks at *m/e* 194, 190, 119, and 265 corresponding to fragments resulting from the cleavage *a* and *b* of the β-lactam XI. The presence of fragments C and D is consistent only with structure XI for the product of the reaction of amidine IX with diphenylketene.



Cycloaddition of diphenylketene with various trisubstituted amidines (XII, XIV, XVI, XVIII, and XX) was attempted. It was possible to prepare analytically pure samples of β-lactams XIX and XXI. A sample of β-lactam XVII, m.p. 108–109°, appeared to be quite pure from the NMR and IR spectra; attempts at further purification led to decomposition. IR spectral evidence (5·7 μ) indicated the formation of two other β-amino-β-lactams (XIII and XV) but neither of them could be isolated as pure compounds.



XII $R_1 = R_3 = R_4 = Me$; $R_2 = H$ XIII

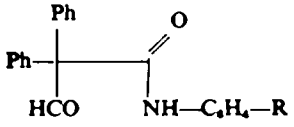
XIV $R_1 = R_3 = Ph$; $R_2 = H$; $R_4 = Me$ XV

XVI $R_1R_2 =$ —CH_2—CH_2—CH_2—CH_2—CH_2—; $R_3 = R_4 = H$ XVII

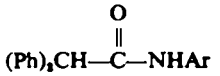
XVIII $R_1R_2 =$ —CH_2—CH_2—CH_2—CH_2—CH_2—; $R_3 = p$—NO_2; $R_4 = H$ XIX

XX $R_1R_2 =$ —CH_2—CH_2—O—CH_2—CH_2—; $R_3 = p$—OMe; $R_4 = Ph$ XXI

The β-lactams XI, XVII, XIX and XXI as other β-amino-β-lactams[2,3] are very sensitive to moisture. The presence of a trace of moisture in the air or in the solvent from which XI, XVII, XIX, and XXI were crystallized causes the opening of the ring and makes the purification of β-amino-β-lactams very difficult. It is interesting that the mode of decomposition of 3,3-diphenyl-4-amino-2-azetidinones XI, XVII, XIX, and XXI is different from that of 3,3-dialkyl-substituted β-lactams.[2,3] We have not detected the presence of the amido aldehyde XXII. Diphenylacetanilide (XXIII) was a product of decomposition of β-lactam XI and XVII. 2,2-Diphenyl-*p*-nitroacetanilide[11] (XXIV) and 2,2-diphenyl-*p*-acetanisidide[12] (XXV) were the de-



XXII



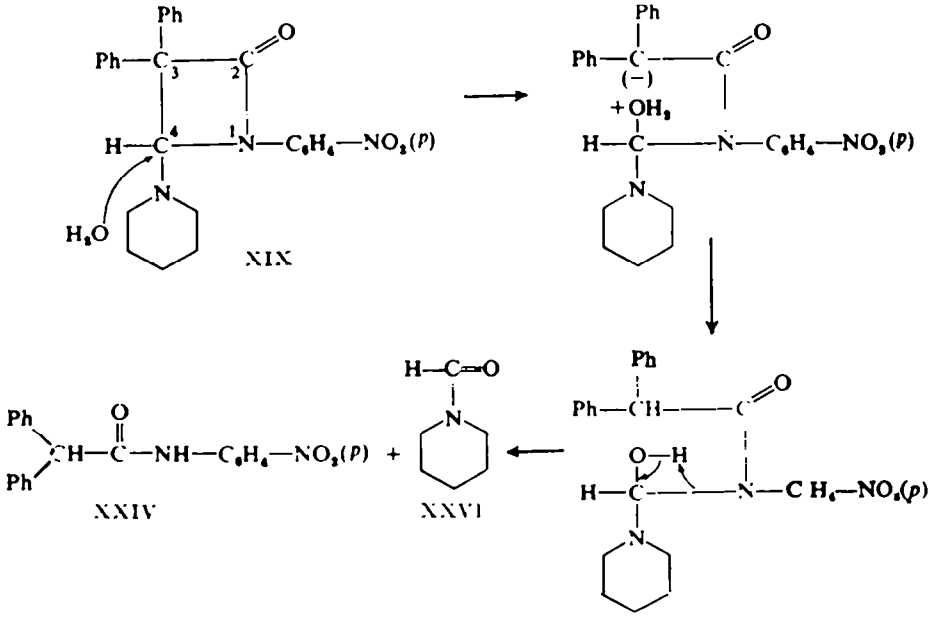
XXIII Ar = Ph

XXIV Ar = (*p*)—NO_2—C_6H_4—

XXV Ar = (*p*)—CH_3O—C_6H_4—

composition products of β-lactams XIX and XXI, respectively. The density of XXIV and XXV was established by the comparison with authentic samples prepared by conventional methods.

The mode of decomposition of β-lactams XI, XVII, XIX, and XXI by the rupture of the bond between carbon-3 and carbon-4 may be explained by the formation of a



XIX

XXIV

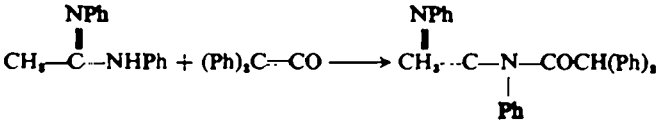
XXVI

[11] J. Woliński, D. Buza, E. Czerwińska-Fejgin and W. Zamlyński, *Chem. Anal.* (Warsaw) **4**, 989 (1959); *Chem. Abstr.* **54**, 17158b (1960).

[12] C. L. Stevens and G. H. Singhal, *J. Org. Chem.* **29**, 34 (1964).

transient carbanion on carbon-3. Such a carbanion is stabilized by a carbonyl and two phenyl groups. A possible mechanism is illustrated by the decomposition of 1-(*p*-nitrophenyl)-3,3-diphenyl-4-piperidino-2-azetidinone (XIX). This mechanism is consistent with the observation that N-formylpiperidine (XXVI) can be isolated along with the amide XXIV as the decomposition products of XIX.

The reaction of amidines with diphenylketene to give 4-amino-2-azetidinones appears to be general for N,N,N′-trisubstituted amidines. As to be expected, the addition of diphenylketene to a disubstituted amidine (viz. XXVII) led only to an amide (XXVIII).



XXVII XXVIII

EXPERIMENTAL

A Perkin–Elmer Infracord was used for routing IR measurement. The IR spectra of new compounds were recorded on a Perkin–Elmer Model 21 spectrophotometer. The NMR spectra were obtained with a Varian DP-60 spectrometer operating at 56·4 Mc or a Varian A-60A spectrometer operating at 60 Mc. TMS served as the internal standard. Broad or complex spectra in the aromatic region are reported as a range, the signals are designated as *c*. Singlet peaks are designated as *s*, doublets as *d*, triplets as *t*, and multiplets as *m*. The mass spectra were obtained with a Consolidated Electrodynamic Corporation mass spectrometer Model No. 21-103C using an all-glass inlet system. The m.ps, obtained on a Fisher-Johns m.p. apparatus are uncorrected. Analytical determinations were performed by Alfred Bernhardt Microanalytisches Laboratorium, Max Planck Institute, Mulheim, West Germany, and by Schwarzkopf Microanalytical Laboratory, Woodside 77, New York.

The preparation of diphenylketene and the reactions of diphenylketene with amidines were carried out in N atm.

Diphenylacetyl chloride.[10] A mixture of 42·4 g (0·2 mole) diphenylacetic acid and 35·6 g (0·3 mole) $SOCl_2$ was heated under reflux on a steam bath for 1 hr. The excess $SOCl_2$ was removed under vacuum. Crystallization from pet. ether yielded 36·5 g (79%) product m.p. 55–57°.

Diphenylketene (X).[10] To a soln of 2·3 g (0·01 mole) diphenylacetyl chloride in 25 ml anhydrous ether, an ether soln (10 ml) of 1·4 g (0·01 mole) tripropylamine was added dropwise. Tripropylamine hydrochloride precipitated as a white solid. The reaction mixture was stored in a tightly stoppered flask overnight in a refrigerator; then it was filtered to obtain a dilute soln. of diphenylketene.

Reaction of diphenylketene with N,N-*dimethyl*-N′-*phenyl-formamidine*

(a) Phenylbenzoyldiazomethane[13] (0·50 g. 2·25 mmole) and N,N-dimethyl-N′-phenylformamidine (0·33 g–2·25 mmole) were dissolved in 25 ml dry hexane and irradiated[14] with uv light for 48 hr. The samples were withdrawn after 4, 11, 27, 34, and 45 hr. for IR studies. The absorption band at 4·88 μ gradually disappeared and the band at 5·67 μ became stronger. After the irradiation was completed, the solvent was removed by evaporation. The IR spectrum of the oily residue did not show absorption at 5·67 μ which indicated that the β-lactam was decomposed.

To a stirred soln of 1·5 g (0·01 mole) N,N,-dimethyl-N′-phenylformamidine in 50 ml of anhydrous ether, an ether soln of diphenylketene was added over a period of 1 hr. After the addition was complete, the reaction mixture was filtered. The IR spectrum of the filtrate showed absorption bands at 5·67 μ and 6·10 μ (unreacted amidine) TLC (carried out on silica gel plate using 30% AcOEt–hexane as developing solvent) indicated the presence of 3 components in the reaction mixture. Column chromatography was also attempted. Florisil was used as the adsorbent, elution was done with hexane and then with hexane–AcOEt solns in ratios of 19:1, 9:1, 4:1, 3:1, 1:1, and finally with

[13] C. D. Nenitzescu and E. Salomonica, *Organic Syn.* **15**, 62 (1935).
[14] W. Kirmse and L. Horner, *Ber. Dtsch. Chem. Ges.* **89**, 2759 (1956).

pure AcOEt. A crystalline material (0·7 g), m.p. 175–177°, was eluted by the 9:1 hexane–AcOEt soln. Recrystallization from AcOEt–hexane yielded a colorless solid, m.p 176–17°, λ_{max}^{nujol} 6·0 μ; MW (mass spectrum) 287. A mixture m.p. with authentic XXIII and the comparison of IR spectra indicated this material to be diphenylacetanilide.

Reaction of diphenylketene with amidine XVI. To a stirred soln of 3·5 g (0·015 mole) amidine[18] (XVI) in 200 ml pet. ether, the soln of diphenylketene (prepared in petr. ether from 3·4 g–0·015 mole diphenyl-acetyl chloride) was added dropwise within 2 hr. The stirring was continued for additional 1½ hr during which period a white solid precipitated. The reaction mixture was stored overnight in a refrigerator and XVII was removed by filtration as a solid (4·45 g–79%), mp 108–108°; μ_{max}^{nujol} 5·72 μ NMR (CD_3Cl) τ: 2·22–2·96 (*c*, 15H); 4·54 (*s*, 1H); 7·42 (*m*, 4H); 8·73 (*m*, 6H). During crystallization the β-lactam XVII was decomposed.

Reaction of diphenylketene with amidine XII *and* XIV. Reaction of diphenylketene with XII and XIV was carried out in a manner similar to that described previously for N,N-dimethyl-N'phenylformamidine (B). The reaction products were viscous liquids, λ_{max}^{nujol} 5·7 μ.

1,3,3-*Triphenyl-4-morpholino-2-azetidinone* (XI). Diphenylketene was prepared from 11·5 g (0·05 mole) diphenylacetyl chloride and 5·5 g (0·05 mole) tripropylamine as described. To a stirred soln of 10·4 g (0·055 mole) IX[18] in 125 ml ether, the ether soln of diphenylketene was added dropwise over a period of 2 hr. The stirring was then continued for an additional 1½ hr. The reaction mixture was filtered and left to stand overnight in the cold when a white solid precipitated. After filtration and crystallization from ether the product was obtained as a colorless solid, m.p. 114–115°; yield 8·5 g (47·9%) (in a second identical procedure, the β-lactam was obtained in 44·2% yield.) Recrystallization from AcOEt–pet. ether did not change the m.p. of the product λ_{max}^{nujol} 5·73 ; NMR ($CDCl_3$), τ: 2·24–294 (*c*, 15H); 4·56 (*s*, 1H); 6·63 (*t*, 4H); 7·42 (*m*, 4H); Mass spectrum: prominent peaks (*m/e*, intensity as % of most intense peak): 266, 11·0 265, 63·8; 205, 11·0; 206, 45; 194, 13·2; 190, 11·0; 189, 6·8; 180, 16; 179, 12·0; 178, 15·3; 166, 18·2; 165, 42·2; 152, 5·2; 151, 3·0; 139, 4·8; 132, 5·2; 130, 9·2; 120, 8·0; 119, 100·0; 115, 8·0; 105, 5·8; 104, 16·0; 103, 11·8; 102·5, 12·2; 102, 16·5; 93, 92·2; 92, 6·0; 91, 64·0; 90, 6·0; 89, 9·2; 88, 5·0; 87, 4·0; 86, 6·0; 85, 5·0; 83, 5·2; 82·5, 9·2; 82, 6·2; 78, 6·0; 77, 31·2; 70, 10·2; 69, 5·5; 68, 5·0. (Found: C, 78·37; H, 6·43; N, 7·24. Cald. for $C_{34}H_{34}N_2O_2$: C, 78·10; H, 6·29; N, 7·29%.)

1-[(N-p-*Nitrophenyl*) *formimidoyl*] *piperidine* XVIII. To a heated soln of 12·4 g (0·11 mole) N-formylpiperidine and 13·8 g (0·1 mole) *p*-nitroaniline in benzene, 16·8 g (0·11 mole) $POCl_3$ was added with caution. The mixture was refluxed on a steam bath for 4 hr. After cooling, the solid amidine hydrochloride was separated by filtration, washed with ether and dissolved in a 20% NaOHaq. The alkaline soln was extracted several times with ether until the ether extract was colorless. The combined ether extract was washed with water and dried over $MgSO_4$. The ether was removed on a rotory evaporator and the solid residue was crystallized from EtOH giving yellow crystals, m.p. 80–82°, yield: 15·0 g (68·7%). An analytical sample obtained by several recrystallizations from EtOH melted at 81–82°. λ_{max}^{nujol} 6·15 μ NMR ($CDCl_3$), τ: 1·94 (*d*, J = 9 c/s 2H); 3·07 (*d*, J = 9 c/s 2H); 2·41 (*s*, 1H); 6·49 (broad, 4H); 8·34 (broad 6H). (Found: C, 61·82; H, 6·19; N, 17·86. Calc. for $C_{18}H_{18}N_4O_3$: C, 61·78; H, 6·48; N, 18·02%.)

1-(p-*Nitrophenyl*)-3,3-*diphenyl-4-piperidino-2-azetidinone* (XIX). The solid product (75% yield) obtained from diphenylketene and XVIII using the same procedure as for XI was crystallized several times from methylene chloride–hexane at room temp. An analytically pure sample, m.p. 91–92°. λ_{max}^{nujol} 5·72 μ; NMR ($CDCl_3$), τ: 1·85 (*d*, J = 9 c/s, 2H); 2·27–276 (*c*, 10H); 4·41 (*s*, 1H); 7·51 (broad, 4H); 8·71 (broad, 6H). (Found: C, 72·65; H, 6·17; N, 10·00. Calc. for $C_{36}H_{35}O_4N_3$: C, 73·05; H, 5·90; N, 9·83%.)

1-(p-*Methoxyphenyl*)-3,3-*Diphenyl-4-morpholino-2-azetidinones* XXI. The procedure for the preparation of XXI was that used for β-lactam IX. Starting from 3·3 g (0·0113 mole) of XXIV, 3·6 g (61%) raw product was obtained. Several crystallizations at room temp from methylene chloride–hexane yielded a colorless, crystalline, analytically pure sample, m.p. 94–95°. λ_{max}^{nujol} 5·74 μ; NMR ($CDCl_3$), τ: 2·64–3·03 (*c*, 15H); 3·49 (*s*, 4H); 6·37 (complex, 7H); 6·59 (*t*, 4H). Mass spectrum: prominent peaks (*m/e*, intensity as % of most intense peaks): 341, 3·5; 296, 1·25; 210, 2·0; 194, 34·2; 167, 48·5; 166, 100·0; 165, 9·0; 164, 8·2; 150, 8·5; 149, 93·0; 139, 12·0; 34, 52·5; 126, 3·0; 121, 6·0; 115, 8·0; 113, 5·0; 106, 7·0; 91, 3·5; 90, 4·0; 88, 5·5; 87, 11·0; 86, 7·5; 83, 16·5; 82, 31·0;

[18] A. Larizza, G. Brancaccio and G. Lettieri, *J. Org. Chem.* 29, 3697 (1964).

81, 19·5; 80, 7·0; 79, 3·5; 78, 3·5. (Found: C, 78·09; H, 6·29; N, 5·87. Calc. for $C_{25}H_{20}N_2O_2$: C, 78·34; H, 6·16; N, 5·71%.)

Reaction of diphenylketene with N,N'-*diphenyl-acetamidine* (XXVII). A soln of diphenylketene (prepared from 2·3 g, 0·001 mole diphenylacetyl chloride) was added to an etheral soln of 2·1 g (0·01 mole) N,N'-diphenyl-acetamidine. The reaction of mixture was left to stand overnight and filtered; the ether was removed on a rotory evaporator. A solid residue (3·2 g) was purified by several crystallizations from EtOH; m.p. 106–107°; λ_{max}^{nujol} 6·0μ; NMR ($CDCl_3$) τ: 3·07 (aromatic, 20H); 4·93 (*s*, 1H); 8·02 (*s*, 3H). (Found: C, 82·77; H, 5·99; N, 7·36. Calc. for $C_{14}H_{24}N_2O$: C, 83·14; H, 5·98; N, 6·93%.)

Note added in proof—After the present work was submitted for publication, we became aware that Opitz and Koch (J. Koch, Sc.D. Thesis, Eberhard-Karls-Universität zu Tübingen, 1965) have studied the reaction of dimethyl ketene with some amidines. The reaction products were not isolated but allowed to react with 2,4-dinitrophenylhydrazine. The derivatives so obtained indicated that β-amino-β-lactams must have been formed in the reaction between the ketene and the amidines.

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