

STUDIES ON LACTAMS—IV¹

A NEW SYNTHESIS OF β -LACTAMS

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Abstract—A synthesis of β -lactams has been achieved using intramolecular Michael addition of a substituted acrylamide of type IV. The scope of the reaction has been studied and the possibility of retro-Michael reaction has been investigated.

THE elucidation of the structure of penicillin led to an interest in β -lactams that has been renewed by the finding that the antibiotic cephalosporin-C also contains the β -lactam ring.² Further attention has been focused on this heterocyclic system by the discovery that some members of this family show interesting physiological activity.³ The feasibility of using β -lactams as monomers for the preparation of polyamides has recently been demonstrated.⁴

The methods of synthesis of β -lactams developed prior to 1945 have been adequately reviewed.⁵ More recent methods have been surveyed by Sheehan and Corey.⁶ Since then Knunyant,⁷ Testa,⁸ Gould,⁹ Ugi,¹⁰ Graf,¹¹ Perelman¹² and Opitz¹³ have developed interesting syntheses for this class of heterocycles.

Previously¹⁴ we have reported a synthesis of the γ -lactam III from the amide I by treatment with a mild base such as triethylamine. A possible mechanism for this reaction was the formation of an acrylamide intermediate II and its subsequent cyclization to III. Compound II prepared by a direct method does not, however, cyclize under these conditions. As the acrylamide might be a comparatively poor Michael acceptor, compound IV was prepared in order to study its cyclization. In this compound the acrylic ester group is a more reactive Michael acceptor than the

¹ Presented at the XIXth International Congress of Pure and Applied Chemistry London, July (1963); A. K. Bose and M. S. Manhas, *Angew. Chem.* **75**, 1026 (1963). Part III, A. K. Bose and M. S. Manhas, *J. Org. Chem.* **27**, 1244 (1962).

² E. P. Abraham and G. G. F. Newton, *Biochem. J.* **58**, 103 (1954).

³ E. Testa, L. Fontanella, G. F. Cristiani and F. Fava, *Liebigs Ann.* **614**, 158 (1958) and other papers in this series.

⁴ R. Graf, G. Lohaus, K. Borner, E. Schmidt and H. Bestian, *Angew. Chem.* (Internat. Edition) **1**, 481 (1962).

⁵ H. T. Clarke, J. R. Johnson and R. Robinson, *The Chemistry of Penicillin*. Princeton University Press (1949).

⁶ J. C. Sheehan and E. J. Corey, *Organic Reactions* **9**, 388 (1959).

⁷ I. L. Knunyant and N. P. Gambaryan, *Izvest. Akad. Nauk S.S.S.R., Otdel. Khim. Nauk* 1037 (1955); *Chem. Abstr.* **50**, 11277 (1956).

⁸ E. Testa and L. Fontanella, *Liebigs Ann.* **625**, 95 (1959).

⁹ F. F. Blicke and W. A. Gould, *J. Org. Chem.* **23**, 1102 (1958).

¹⁰ I. Ugi, *Angew. Chem.* **74**, 9 (1962).

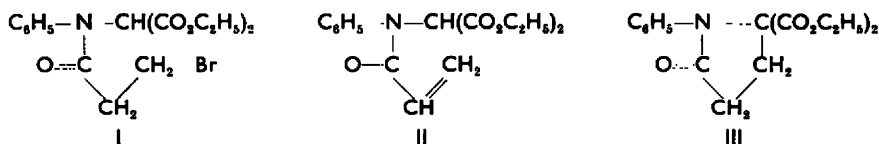
¹¹ R. Graf, *Liebigs Ann.* **611**, 111 (1963).

¹² M. Perelman and S. A. Mizsak, *J. Amer. Chem. Soc.* **84**, 4988 (1962).

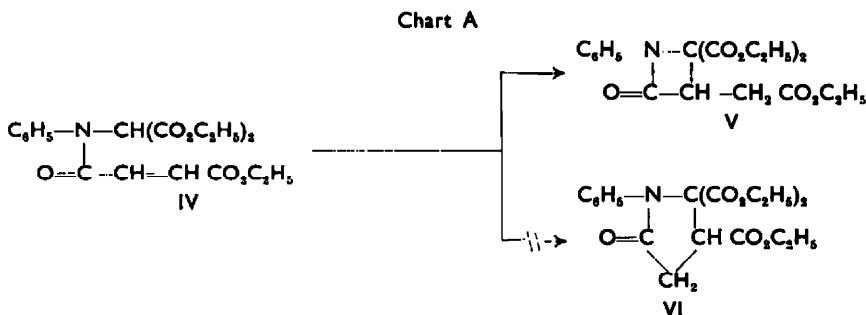
¹³ G. Opitz and J. Koch, *Angew. Chem.* **75**, 167 (1963).

¹⁴ A. K. Bose, B. N. Ghosh-Mazumdar and B. G. Chatterjee, *J. Amer. Chem. Soc.* **82**, 2382 (1960), A. K. Bose and M. S. Manhas, *J. Org. Chem.* **27**, 1244 (1962).

acrylamide function. The chart A indicates that if IV undergoes internal Michael addition it will yield the β -lactam V rather than the γ -lactam VI which may be expected if the cyclization proceeds under the electron-withdrawing influence of the



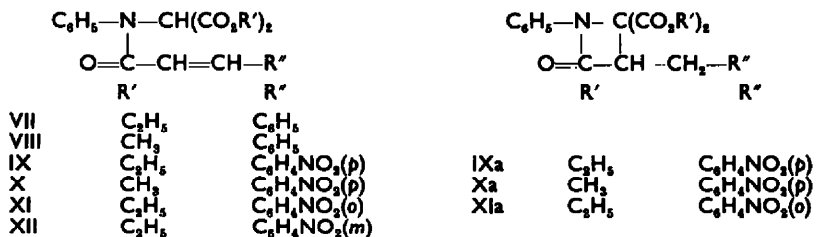
carbonyl group of the amide. Amide IV fails to cyclize with triethylamine. But when piperidine was used as the base, a thick, oily product was obtained which could not be adequately purified. The IR and NMR spectra of this liquid show that cyclization of IV to the β -lactam V has taken place.



Other electron withdrawing groups in the β -position of the acrylic acid function were studied for preparing β -lactams by this method. The amides VII and VIII corresponding to cinnamic acid fail to cyclize. Attempts were then made to introduce more electronegative substituents in the β -position of the amide to study their effect on cyclization. The *p*-nitrophenyl group is the most useful.

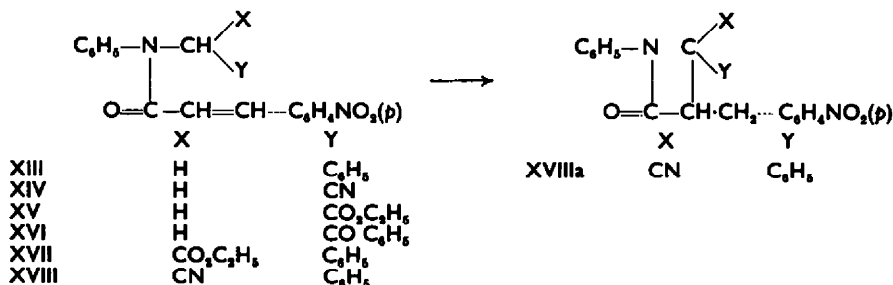
Under the influence of piperidine the amides IX, X and XI give the β -lactams IXa, Xa and XIa respectively. The structure of the cyclized products was confirmed by their elemental analysis and IR and NMR spectra.

The failure of the amide XII to cyclize can be attributed to the lack of activation by the nitro group which is now in the *meta* position.



The scope of this reaction was further extended by studying changes in the malonic ester moiety of the amide. The amides XIII–XVIII were prepared and their cyclization studied. It was noticed that with amides XIII, XIV, XV and XVI with only one activating group (Y), no cyclization occurs when piperidine is used as a catalyst. The amide XVII with phenyl and carbethoxy groups as the substituents also fails to

cyclize. However, amide XVIII with phenyl and cyano groups cyclizes to give the β -lactam (XVIIIa). This may be ascribed to the greater electron-withdrawing power of the cyano group as compared with the carboxy group.



The effect of various bases as catalysts in the cyclization to β -lactams was also studied. Amide X in methylene chloride solution was treated with quinoline, pyridine, pyrrole, triethylamine, piperidine, methanolic sodium methoxide, methanolic sodium hydroxide or potassium t-butoxide. The reaction mixtures were kept at room temperature for 48 hr. In no one case was cyclization to the β -lactam observed. Piperidine and methanolic sodium methoxide caused decomposition of the amide yielding an intractable tarry material; in all other cases the starting material was recovered. The effectiveness of these bases for the cyclization of X was then studied in dioxane solution. Methanolic sodium hydroxide gives a tarry material with no discernible IR spectrum. Potassium t-butoxide affords a high melting solid insoluble in common organic solvents. The IR spectrum shows a strong peak at 6.0 μ (amide carbonyl), but the 6.1 μ peak (unsaturation) present in the starting material has disappeared indicating the polymerization of the amide. Other bases have no effect and the starting material was recovered.

The possibility of the reversion of the β -lactams IXa and Xa to the amides IX and X due to the retro-Michael reaction was investigated. The amides IX and X show strong UV absorption peaks at 309 $m\mu$ (ϵ 23,690) and 311 $m\mu$ (ϵ 22,671) respectively whereas the corresponding β -lactams IXa and Xa have strong absorption maxima at 253 $m\mu$ (ϵ 17,649) and 250 $m\mu$ (ϵ 14,945) respectively.

To each of the β -lactam solutions a drop of dilute hydrochloric acid was added and their spectra noted at different intervals of time. No shift was found in the UV peaks of the lactams even after 48 hr, indicating that the β -lactam is stable to the action of dilute hydrochloric acid.

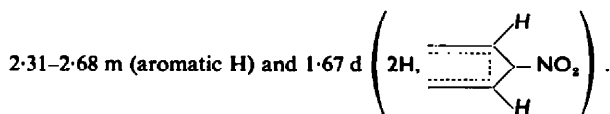
When, however, the solution of the β -lactam IXa is refluxed with one equivalent of sodium ethoxide for 1 hr, the product shows the appearance of a 309 $m\mu$ peak besides the 253 $m\mu$ maxima in the UV spectrum. This is indicative of the partial cleavage of the β -lactam ring to the corresponding amide. These results are corroborated by the IR spectrum of the product which shows peaks at 5.65 μ (β -lactam carbonyl), 5.75 μ (ester carbonyl), 6.0 μ (amide carbonyl) and a shoulder at 6.1 μ (α,β -unsaturation).

Similar occurrence of the retro-Michael reaction under basic conditions may be observed when to a solution of the β -lactam IXa a drop of piperidine is added and the UV spectrum recorded at different intervals of time. After 24 hr, a shoulder at 311 $m\mu$ is noticeable in the spectrum.

1-Phenyl-3-p-nitrobenzyl-4,4-dicarbethoxy-2-azetidinone (IXa). To a solution of 1 g of IX in 25 ml dioxane was added 1 ml piperidine. The original pale yellow solution immediately turned reddish brown. It was allowed to stand at room temp overnight. The dioxane was then evaporated. The residue was taken up in ether, washed several times with water and dried (MgSO₄). On evaporating the ether under red. press., 0.94 g (94%) pale yellow solid was obtained. It was crystallized from ether as small needles, m.p. 119°. $\lambda_{\text{max}}^{\text{nujol}}$ 5.6 μ , β -lactam carbonyl; 5.75 μ , ester carbonyl. (Found: C, 62.21; H, 5.16; N, 6.58. Calc. for C₂₂H₂₂N₂O₇: C, 61.96; H, 5.20; N, 6.57%).

Dimethyl compound (Xa), m.p. 166.5–167° (74% yield). Chemical shift (in τ units) of NMR

signals*: 5.60 t (1H, —C—CH₂—); 6.69 d (2H, —CH—CH₂—C₆H₄—); 6.09 s (6H, —C(=O)—O—CH₃)



(Found: C, 59.99; H, 4.62; N, 7.17. Calc. for C₂₀H₁₈N₂O₇: C, 60.30; H, 4.55; N, 7.03%).

Diethyl N-[β -(*o*-nitrophenyl)acryloyl]anilinomalonate (XI). *o*-Nitrocinnamic acid (1.93 g, 0.01 mole) was added to a solution of diethylanilinomalonate (2.51 g, 0.01 mole) in dioxane (30 ml). This mixture was refluxed with 3 ml PCl₅ for 4 hr. Dioxane was then removed at the pump. The ether extract of the residue afforded 3.9 g (91%) of product which on crystallization from EtOH–ligroin gave 3.1 g of the amide XI, m.p. 88°. $\lambda_{\text{max}}^{\text{nujol}}$ 5.7 μ , ester carbonyl; 6.0 μ , amide carbonyl. (Found: C, 62.01; H, 5.28; N, 6.77. Calc. for C₂₂H₂₂N₂O₇: C, 61.96; H, 5.2; N, 6.57%).

1-Phenyl-3-*o*-nitrobenzyl-4,4-dicarbethoxy-2-azetidinone (XIa). Diethyl N-[β -(*o*-nitrophenyl)acryloyl]anilinomalonate (1 g) was dissolved in 25 ml ether and 1 ml piperidine added. The solution was allowed to stand overnight and then washed with water and dried (MgSO₄). Evaporation of the solvent under red. press. gave 0.7 g (70%) β -lactam. It was crystallized from EtOH–MeOH, m.p. 78°, $\lambda_{\text{max}}^{\text{nujol}}$ 5.65 μ , β -lactam carbonyl; 5.75 μ , ester carbonyl. (Found: C, 62.10; H, 5.39; N, 6.57. Calc. for C₂₂H₂₂N₂O₇: C, 61.96; H, 5.20; N, 6.57%).

Diethyl N-[β -(*m*-nitrophenyl)acryloyl]anilinomalonate (XII). A solution of 2.51 g (0.01 mole) diethyl anilinomalonate in 30 ml dioxane was refluxed for 4 hr with 1.93 g (0.01 mole) *m*-nitrocinnamic acid and 3 ml PCl₅. The dioxane was then removed under red. press. The chloroform extract of the residue gave 3.5 g (83%) crude amide XII which was crystallized from ethyl acetate–ligroin as pale yellow needles, m.p. 119°. $\lambda_{\text{max}}^{\text{nujol}}$ 5.75 μ , ester carbonyl; 6.0 μ , amide carbonyl. (Found: C, 62.20; H, 5.39; N, 6.62. Calc. for C₂₂H₂₂N₂O₇: C, 61.96; H, 5.2; N, 6.57%).

A sample of the amide in dioxane solution was treated with piperidine. After 2 days the unchanged amide was recovered.

N-Benzyl- β -(*p*-nitrophenyl)acryloyl anilide (XIII). Benzylaniline¹⁷ (5 g) and *p*-nitrocinnamic acid (5.3 g) were dissolved in 40 ml dioxane and 3.7 g PCl₅ gradually added. The mixture was then refluxed overnight. Removal of dioxane under red. press. gave a brown tarry material which was extracted with benzene. The benzene solution yielded 5.79 g (53%) of the amide XIII as a thick, brown mass which solidified on standing. Recrystallization from EtOH gave fine needles; m.p. 130°; $\lambda_{\text{max}}^{\text{nujol}}$ 6.0 μ (amide carbonyl). (Found: C, 74.04; H, 4.52; N, 7.82. Calc. for C₂₂H₁₈N₂O₅: C, 73.73; H, 5.06; N, 7.82%).

The amide (1 g) was dissolved in about 10 ml benzene and 0.5 ml piperidine added. The solution was allowed to stand for 2 days at room temp and then washed with water and dried (MgSO₄). Removal of benzene gave an oil which was dissolved in methylene chloride and filtered through a column of alumina. Evaporation of the methylene chloride gave the unchanged amide.

N-Cyanomethyl-(*p*-nitrophenyl)acryloyl anilide (XIV). Anilinoacetonitrile¹⁸ (2 g) and *p*-nitrocinnamic acid (3 g) were dissolved in 25 ml dioxane and 2 g PCl₅ added. The solution was refluxed overnight and the dioxane then evaporated leaving a black tarry residue which was extracted with

¹⁷ F. G. Willson and T. S. Wheeler, *Organic Syntheses* 8, 38 (1928).

¹⁸ C. Engler, *Ber. Dtsch. Chem. Ges.* 6, 1004 (1873).

methylene chloride. The crude product was crystallized from ethyl acetate-ligroin to afford the amide as small needles (1.52 g, 33%), m.p. 154°. $\lambda_{\text{max}}^{\text{nujol}}$ 6.0 μ , amide carbonyl. (Found: C, 65.78; H, 4.24; N, 13.78. Calc. for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_3$: C, 66.44; H, 4.26; N, 13.68%).

To 0.6 g of the amide in about 15 ml benzene, was added 0.5 ml piperidine and the solution allowed to stand at room temp for 2 days. The product was found to be the unchanged amide on the basis of its m.p. and IR spectrum.

Ethyl N- β (p-nitrophenyl)acryloyl-N-phenyl glycine (XV). A solution of 1 g ethyl anilinoacetate¹⁹ in 30 ml dioxane was refluxed with 1.3 g *p*-nitrocinnamic acid and 1 ml PCl_5 for 4 hr. Dioxane was then removed at the pump and the residue extracted with methylene chloride yielding 1.1 g (55% based on ethylanilino acetate) of the amide XV. Recrystallization from ethyl acetate-ligroin gave colourless needles, m.p. 112–113°. (Found: C, 64.35, H, 5.14, N, 7.90. Calc. for $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}_5$: C, 64.40; H, 5.12; N, 7.91%).

To a solution of 0.5 g ethyl *N- β (p-nitrophenyl)acryloyl anilinoacetate* in 10 ml dioxane was added 0.5 ml piperidine. The solution was kept at room temp for 2 days and then the dioxane evaporated under red. press. The residue was extracted with ether, washed several times with water and finally dried (Na_2SO_4). Unchanged amide was recovered after removal of the solvent under red. press.

N-Phenacyl-p-nitrocinnamanilide (XVI). A mixture of 2.11 g (0.01 mole) *N*-phenacylaniline,²⁰ 2.0 g (0.01 mole) *p*-nitrocinnamic acid, 1 ml PCl_5 and 100 ml tetrahydrofuran was refluxed on an oil bath for 4 hr. Removal of the solvent under red. press. gave a yellow solid which was extracted with methylene chloride and the product crystallized from EtOH-ethyl acetate as cream coloured flakes of the amide XVI, m.p. 180–181° (2.28 g; 59%). $\lambda_{\text{max}}^{\text{EtOH}}$ 313 μm , ϵ 24,600; 242 μm , ϵ 22,600. $\lambda_{\text{max}}^{\text{nujol}}$ 6 μ , amide carbonyl. (Found: C, 71.23; H, 4.68; N, 7.26. Calc. for $\text{C}_{22}\text{H}_{18}\text{N}_2\text{O}_4$: C, 71.49; H, 4.7; N, 7.25%).

A dioxane solution of 0.5 g amide XV and 4 drops piperidine were allowed to stand at room temp for 48 hr but after the usual work up, only unchanged amide was recovered.

Ethyl N-(p-nitrocinnamyl)anilinophenylacetate (XVII). Ethyl α -anilinophenyl acetate²¹ (10.2 g; 0.04 mole), *p*-nitrocinnamic acid (7.32 g, 0.04 mole), PCl_5 (2.9 ml) and 100 ml dry dioxane were mixed and refluxed with stirring for 4 hr. Upon removing the solvent under red. press., a thick, brown oil was left which solidified on standing. Crystallization of this solid from alcohol afforded 6.72 g amide as yellow needles, m.p. 173°. $\lambda_{\text{max}}^{\text{nujol}}$ 5.95 μ , amide carbonyl. (Found: C, 69.89; H, 5.37; N, 6.65. Calc. for $\text{C}_{28}\text{H}_{22}\text{N}_2\text{O}_5$: C, 69.75; H, 5.15; N, 6.51%).

N-(α -Cyanobenzyl)-p-nitrocinnamanilide (XVIII). A mixture of anilinophenylacetone nitrile²² (1.17 g), *p*-nitrocinnamic acid (1.09 g), PCl_5 (1 ml) and dioxane (20 ml) was refluxed with stirring for 3 hr. The solvent was then stripped off the dark brown reaction mixture on a steam bath under vacuum. The residual brown, viscous oil was extracted with benzene and yielded a viscous oil which solidified to an orange solid (1.32 g, 61%). Upon crystallization from 95% EtOH, the amide XVIII was obtained as needles, m.p. 161–162°, $\lambda_{\text{max}}^{\text{nujol}}$ 6.0 μ (amide carbonyl), 6.14 μ , conjugated double bond. (Found: C, 72.25; H, 4.77; N, 11.19. Calc. for $\text{C}_{28}\text{H}_{17}\text{N}_3\text{O}_3$: C, 72.05; H, 4.47; N, 10.96%).

1,4-Diphenyl-3-p-nitrobenzyl-4-cyano-2-azetidione (XVIIIa). To a solution of 0.33 g *N-(α -cyanobenzyl)-p-nitrocinnamanilide* in 10 ml dichloromethane were added 5 drops piperidine and the mixture allowed to stand at room temp for 9 days. It was then washed several times with water until the washings were neutral to litmus. The organic layer was dried (MgSO_4) and stripped of solvent under vacuum giving 0.16 g (48.5%) viscous oil which solidified to an orange solid. It was crystallized from ethyl acetate-pet. ether, m.p. 157–159°. $\lambda_{\text{max}}^{\text{CH}_2\text{Cl}_2}$ 5.61 μ , β -lactam, 6.21 μ , *N*-phenyl, 6.54 μ and 7.42 μ , conjugated nitro. (Found: C, 71.61; H, 4.82; N, 10.65. Calc. for $\text{C}_{28}\text{H}_{17}\text{N}_3\text{O}_3$: C, 72.05; H, 4.47; N, 10.96%).

Dimethyl N-(p-nitrocinnamyl)- β -anilinobenzylmalonate (XIX). *p*-Nitrocinnamic acid (4 g), thionyl chloride (5 ml) and dioxane (15 ml) were heated under reflux for 4 hr. Excess solvent and thionyl chloride were removed under red. press. on a steam bath. The resulting yellow solid (*p*-nitrocinnamyl chloride) was taken up in 30 ml methylene chloride and added dropwise with stirring to a solution of 6.26 g dimethyl- β -anilinobenzylmalonate²³ in 9.82 g pyridine and 20 ml methylene chloride cooled

¹⁹ T. Curtius, *J. Prakt. Chem.* **38**, 436 (1888).

²⁰ P. E. Verkade and E. F. J. Janetsky, *Rec. Trav. Chim.* **62**, 763 (1943).

²¹ C. A. Bischoff, *Ber. Dtsch. Chem. Ges.* **30**, 2305 (1897).

²² E. Knovengel, *Ber. Dtsch. Chem. Ges.* **37**, 4083 (1904).

²³ E. J. Wayne and J. B. Cohen, *J. Chem. Soc.* **127**, 459 (1925).

in an ice-water bath. Stirring was continued for an additional hr and the mixture then filtered to remove insoluble material (*p*-nitrocinnamanilide, m.p. 204–206°, lit.²⁴ m.p. 208°) formed during the course of the reaction. The filtrate was washed with 10% NaHCO₃ aq. dil. HCl and water respectively. The methylene chloride layer was dried (MgSO₄) and removal of the solvent gave 8.69 g of a thick amber coloured oil which solidified on standing. Repeated crystallization from ether–ligroin gave 7.27 g (76.5%) of the amide, m.p. 144–145°. $\lambda_{\max}^{\text{nujol}}$ 5.7 μ , ester carbonyl; 6.0 μ , amide carbonyl; 6.1 μ , conjugated unsaturation. (Found: C, 66.65; H, 4.94; N, 5.76. Calc. for C₂₇H₂₄N₂O₇: C, 66.38; H, 4.95; N, 5.74%).

1,5-Diphenyl-3-(*p*-nitrobenzyl)-4,4-dicarbomethoxy pyrrolidinone (XXI). *t*-Butyl alcohol (1 ml) containing a pinch of NaH was added to a solution of 200 mg (0.41 mmoles) dimethyl-*N*-(*p*-nitrocinnamyl)- β -anilinobenzylmalonate in 10 ml tetrahydrofuran. After 10 hr, the solvent was removed on a steam bath under red. press. The resulting thick tan oil was taken up in ether and filtered. The filtrate was washed with water. The organic layer was dried (MgSO₄) and stripped of solvent under red. press. affording 210 mg of a yellow solid. Crystallization from ethyl acetate–pet. ether gave the colourless crystalline product XXI, m.p. 156–157°, $\lambda_{\max}^{\text{EtOH}}$ 270 μ (ϵ 12,600), Sh 242 $m\mu$ (ϵ 10, 100) and Sh 220 $m\mu$ (ϵ 15,000). $\lambda_{\max}^{\text{CH}_2\text{Cl}_2}$ 5.74 μ (ester carbonyl), 5.83 μ , γ -lactam carbonyl; 6.55 μ and 7.42 μ , nitro. (Found: C, 66.55; H, 5.04; N, 5.81. Calc. for C₂₇H₂₄N₂O₇: C, 66.38; H, 4.95; N, 5.74%).

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²⁴ E. A. Smirnov; *J. Gen. Chem., USSR* 10, 43 (1940); P. J. Ittyerah and K. C. Pandya, *Proc. Indian Acad. Sci.* 13A, 119 (1941).

²⁵ National Science Foundation undergraduate research participant.