INDOLE DERIVATIVES

LX * SYNTHESIS OF β-LACTAMS OF THE INDOLE SERIES

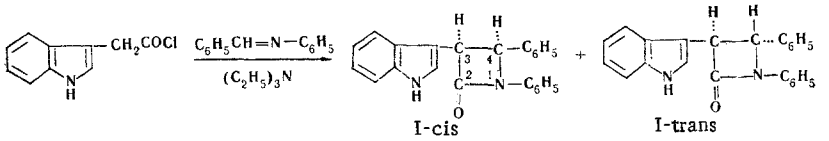
A. K. Mukerdzhi and N. N. Suvorov

UDC 547-318'752

The synthesis of β-lactams containing an indole ring was accomplished by the reaction of acyl chlorides with Schiff bases in the presence of triethylamine. 3-Indolylacetyl chloride reacts with benzylideneaniline to give a mixture of cis- and trans-β-lactams. Schiff bases obtained from N-substituted indole-3-aldehyde and aniline derivatives form phthalimido-β-lactams by reaction with phthalimidoacetyl chloride, while the azomethines of indole-3-aldehyde itself are acylated at the NH group under these conditions. Hydrazinolysis of the phthalimido-β-lactams gives amino-β-lactams. The reaction of 3-[β-(benzylideneamino) ethyl]indole and phthalimidoacetyl chloride leads to a β-lactam and a carboline derivative, the yields of which depend on the order of addition of the reacting compounds. The configurations of the β-lactams were established from the NMR data.

The steroid alkaloids pakistermin-A and pakistermin-B contain β-lactam rings [1]; this has again intensified interest in β-lactams [2], which have acquired special significance since the discovery of penicillin [3-6] and cephalosporin C [7,8]. A large number of β-lactams have been obtained, but their indole analogs are still unknown.

To synthesize indole β-lactams we selected the reaction of acyl chlorides with Schiff bases in the presence of triethylamine. Thus 3-indolyacetyl chloride reacts with benzylideneaniline in the presence of triethylamine to give a mixture of the cis and trans isomers of the corresponding β-lactams (I):



I-cis I-trans

If azomethine II is used as the Schiff base, the NH group of the indole portion of the molecule is acylated under the conditions selected by us. The structure of the N-acyl derivative (IV) thus obtained was confirmed by alternative synthesis, i.e., by condensation of N-acetylindole-3-aldehyde with aniline.

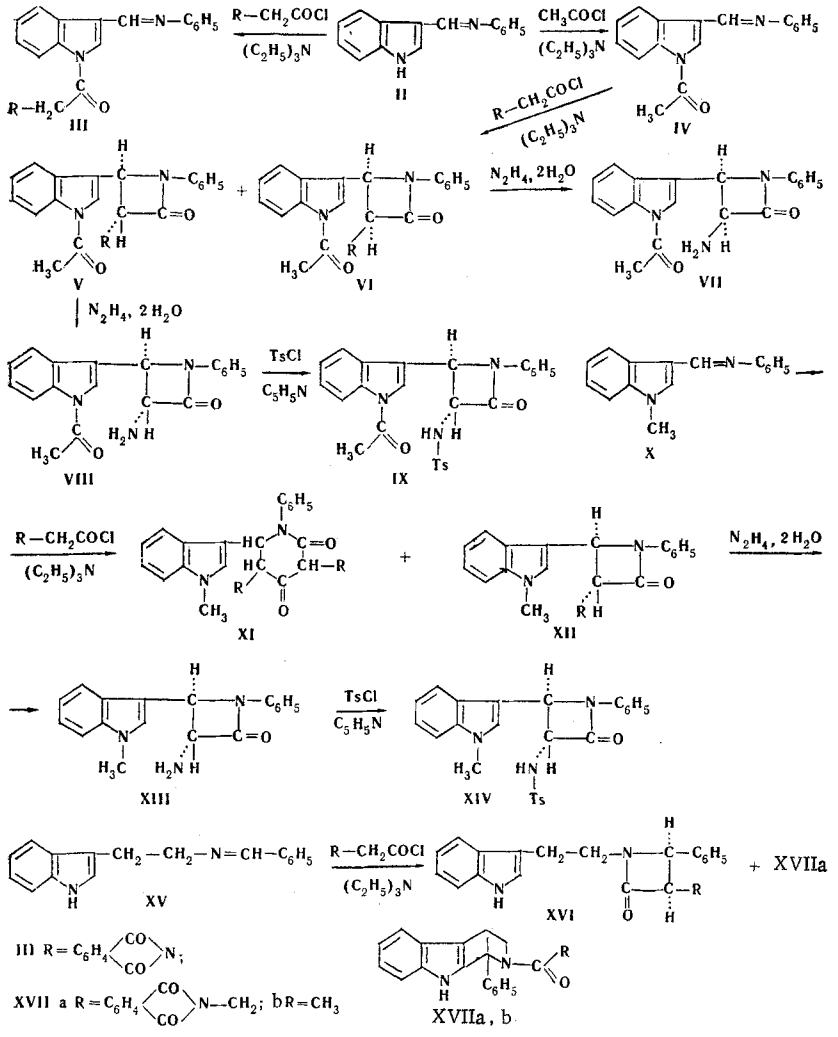
If, however, the NH group is protected by methylation or acetylation, phthalimido-β-lactams are formed by reaction with phthalimidoacetyl chloride via the method in [9]. Thus cis- (VI) and trans-phthalimido-β-lactams (V) are obtained from IV, while trans-phthalimido-β-lactam XII, 2,4-diketopiperidine derivative XI (confirmed by IR and mass spectra), and traces of an unidentified substance are obtained from X. The yields of XI and XII depend on the sequence in which the reacting substances are added and on the concentration.

The stereochemistry of the β-lactams obtained was established on the basis of a determination of the spin-spin coupling constants of the C_3 and C_4 protons in the NMR spectra. According to the data in [2,10], J = 5-6 Hz for cis β-lactams, while J = 2.0-2.5 Hz for the trans configuration. The trans configuration (J =

*See [18] for Communication LIX.

D. I. Mendeleev Moscow Chemical-Engineering Institute. Translated from Khimiya Geterotsiklichesкikh Soedinenii, No. 12, pp. 1626-1630, December, 1970. Original article submitted July 27, 1969.

2 Hz) was assigned to VIII, IX, XII, and XIV, while the cis configuration (J = 6 Hz) was assigned to VII and XIV. I is a mixture of approximately equal amounts of the cis and trans isomers since the C_3 and C_4 proton signals in the NMR spectrum form AB systems with chemical shifts δ_3 = 5.22 ppm, δ_4 = 5.51 ppm and spin-spin coupling constant J = 5.5 Hz (cis isomer), and δ_3 = 4.44 ppm, δ_4 = 5.00 ppm, and J = 2.5 Hz (trans isomer).



The phthalimido-β-lactams were subjected to hydrazinolysis via the method in [9] with a somewhat modified procedure. While VIII can be obtained in pure form, XIII could be isolated only in the form of the N-tosyl derivative (XIV) or the adipiate. The IR and NMR spectra confirmed the structure of VII, but it could not be isolated in analytically pure form nor could the corresponding derivative be obtained.

V and VI are slightly soluble in the usual solvents, and this made it impossible to obtain their NMR spectra.

trans-Amino-β-lactam VIII and cis-amino-β-lactam VII were obtained without traces of the other isomers by hydrazinolysis of V and VI, respectively. Consequently, V has the trans configuration, and VI has the cis configuration. Although there are data on epimerization in the β-lactam ring of penicillin [11, 12], the interconversion of the cis and trans isomers for our compounds is nevertheless unlikely in view of steric hindrance. Bose et al. [2] checked this possibility in a similar case and found that this sort of transformation does not occur. In addition, trans-phthalimido-β-lactam XII gave exclusively trans-tosylamino-β-lactam XIV by hydrazinolysis and preparation of the sulfonamide.

The addition of phthalimidoacetyl chloride to a benzene solution of benzylidenetryptamine (XV) in the presence of triethylamine resulted in the formation of only the cis-β-lactam (XVI). However, carboline

TABLE 1. β-Lactams of the Indole Series

Compound	Mp, °C	Empirical formula	Found, %			Calc., %			Yield, %
			C	H	N	C	H	N	
I	142—144	$C_{23}H_{18}N_2O$	81,66	5,58	8,35	81,65	5,32	8,28	12
V	263—264	$C_{27}H_{19}N_3O_4$	71,90	4,28	9,12	72,16	4,23	9,35	32
VI	234—236	$C_{27}H_{19}N_3O_4$	72,51	4,47	9,34	72,16	4,23	9,35	5,5
VIII	87—90 dec	$C_{19}H_{17}N_3O_2$	71,45	5,63	13,02	71,47	5,32	13,16	33
IX	219—220	$C_{26}H_{23}N_3O_4$	66,03	5,00	8,75	65,96	4,86	8,87	44
XII	202—204	$C_{26}H_{19}N_3O_3$	74,22	4,21	9,59	74,10	4,51	9,97	75
XII	195—197	$C_{26}H_{19}N_3O_3 \cdot 1/2H_2O$	72,56	4,92	9,50	72,55	4,65	9,50	—
XIII	140—142 dec	$2C_{18}H_{17}N_3O \cdot C_6H_{10}O_4$	69,07	6,26	11,55	69,23	6,04	11,53	26
XVI	224—226	$C_{27}H_{21}N_3O_3$	74,77	5,21	9,71	74,48	4,82	9,65	62
XIV	175	$C_{25}H_{23}N_3O_3$	67,22	5,05	9,14	67,41	5,16	9,43	22

*The data for the adipic acid salt are presented.

derivative XVIIa was obtained together with a small amount of cis-β-lactam when the order of addition of the reacting compounds was changed. Carboline derivative XVIIb was similarly formed in the case of acetyl chloride. The IR spectra ($CHCl_3$) of XVIIa and b contain four peaks at 1660 and 1635 cm^{-1} (tertiary amide) and at 3480 cm^{-1} (NH).

Ring cleavage occurs during the hydrazinolysis of β-lactam XVI.

EXPERIMENTAL

The IR spectra were obtained with a UR-10 spectrophotometer, while the NMR spectra were obtained with a JNM-4H-100 spectrometer. The melting points of the β-lactams and the results of elementary analysis are presented in Table 1.

1,4-Diphenyl-3-(3-indolyl)azetidin-2-one (I). A solution of 1.9 g (0.001 mole) of 3-indolylacetyl chloride [13] in 30 ml of dry ether was added dropwise with stirring to a solution of 1.8 g (0.001 mole) of benzylideneaniline and 1.5 ml (0.001 mole) of triethylamine in 30 ml of dry ether at room temperature. The stirring was continued for another 2 h, and the mixture was allowed to stand overnight at room temperature. The solvent was removed, and the viscous mass was extracted with benzene. The benzene extract was introduced into a column packed with neutral aluminum oxide and eluted with benzene followed by ether. The solvent was removed from the eluates in vacuo, and the residue was recrystallized from benzene–petroleum ether to give 0.4 g of I. IR spectrum (CCl_4): 3500 cm^{-1} (NH), 1760 cm^{-1} (β-lactam C = O).

Preparation of Schiff Bases from Indole-3-aldehyde and Aniline. The following method was used to prepare II [14], IV, and X. Equimolar amounts of indole-3-aldehyde [15], N-acetylindole-3-aldehyde [14], and N-methylindole-3-aldehyde [16], respectively, were refluxed with aniline in benzene (10 ml per gram of aldehyde) with a Dean–Stark adapter. To obtain II and X it is necessary to add catalytic amounts of glacial acetic acid to bring about the reaction. At the end of the reaction the solvent was removed in vacuo and a small amount of alconol was added to isolate the precipitate.

1-Acetylskatylideneaniline (IV). This was obtained in 50% yield and had mp 136-137 deg (from alcohol). Found %: C 77.47; H 5.50; N 10.64. $C_{17}H_{14}N_2O$. Calc. %: C 77.86; H 5.33; N 10.68.

1-Methylskatylideneaniline (X). This was obtained in 60% yield and had mp 128-130 deg (from alcohol). Found %: C 82.04; H 6.35; N 12.10. $C_{16}H_{14}N_2$. Calc. %: C 82.05; H 5.98; N 11.95. IR spectrum ($CHCl_3$): 1625 cm^{-1} (C=N).

1-Phthalimidoacetylskatylideneaniline (III). This was synthesized by adding phthalimidoacetyl chloride to skatylideneaniline (II) at room temperature in the presence of triethylamine via method A (see below). The product was obtained in 31% yield and had mp 209-212 deg (from benzene). IR spectrum ($CHCl_3$): 1625 cm^{-1} (C=N). Found %: C 73.55; H 4.13; N 10.41. $C_{25}H_{17}N_3O_3$. Calc. %: C 73.73; H 4.17; N 10.31.

Phthalimido-β-lactams (Method A). A solution of 17.87 g (0.08 mole) of phthalimodoacetyl chloride in 200 ml of dry benzene was added dropwise with stirring to a solution of 20.9 g (0.08 mole) of 1-acetylskatylideneaniline (IV) and 12 ml (0.08 mole) of triethylamine in 400 ml of dry benzene at 40-50 deg. At the

end of the addition, stirring was continued for 1 h at 40-50 deg, after which the mixture was refluxed for 30 min and cooled. The resulting precipitate was filtered, washed twice with dry benzene (20-ml portions), dried, and treated with water to dissolve the triethylamine hydrochloride. The residue was filtered and washed several times with water to give 10.1 g of a product with mp 258-260 deg (dec.). The benzene filtrate was distilled to dryness in vacuo, and 200 ml of alcohol was added to the residual viscous mass. This mixture was refluxed for 30 min and then filtered while hot. The residue on the filter was washed twice with boiling ethanol (20-ml portions) to give 1.2 g of a substance with mp 257-260 deg. The overall yield of unpurified trans-lactam V was thus 11.53 g (31.5%) with mp 263-264 deg (from aqueous acetone). IR spectrum ($CHCl_3$): 1720 cm^{-1} (C=O) of the phthalimido and N-acetyl groups) 1765-1780 cm^{-1} (C=O) of the β-lactam phthalimido groups). A very impure substance precipitated from the alcohol extract. Repeated recrystallization from chloroform–petroleum ether gave 2 g (5.5%) of cis-lactam VI with mp 234-236 deg. IR spectrum ($CHCl_3$): 1720 cm^{-1} (C=O) of the phthalimido and N-acetyl groups), 1765-1780 cm^{-1} (C = O) of the β-lactam and phthalimido groups).

Method B. Phthalimidoacetyl chloride [4.47 g (0.02 mole)] in 70 ml of dry benzene was added drop wise with vigorous stirring to a solution of 4.682 g (0.02 mole) of 1-methylskatylideneaniline (X) in 100 ml of dry benzene at 60 deg, and the mixture was stirred for 30 min. A solution of 4.5 ml (0.02 mole) of triethylamine in 20 ml of dry benzene was then added dropwise, after which the mixture was refluxed under low heat for 1 h and allowed to stand overnight at room temperature. The resulting precipitate was filtered, washed with benzene, dried, and washed with water to give 6.3 g (75%) of trans-β-lactam XII. This was recrystallized from aqueous acetone and dried at 100 deg in vacuo for 48 h to give a product with mp 202-204 deg. IR spectrum $CHCl_3$: 1720 cm^{-1} (C=O) of the phthalimido group), 1765-1780 cm^{-1} (C=O) of the β-lactam and phthalimido groups). NMR spectrum ($CDCl_3$): δ 3.55 (CH_3), 5.48 (3-CH), 5.58 ppm (4-CH), J = 2.5 Hz.

1-Phenyl-2,4-diketo-3,5-diphthalimido-6-(1-methyl-3-indolyl)piperidine (XI). Phthalimidoacetyl chloride [22.35 g (0.1 mole)] dissolved in 70 ml of dry benzene was added gradually with stirring to a refluxing solution of 23.4 g (0.1 mole) of 1-methylskatylideneaniline (X) and 15 ml (0.1 mole) of triethylamine in 300 ml of dry benzene. At the end of the addition the mixture was refluxed under low heat for 1 h and a allowed to stand overnight at room temperature. Subsequent workup gave 30 g of a yellow preparation. Fractional crystallization from chloroform-benzene gave 12 g of trans-lactam XII and 3 g (9.8%) of XI with mp 254-256 deg. After recrystallization from acetone it melted at 254-256 deg. IR spectrum ($CHCl_3$); 1720 and 1780 cm^{-1} (C=O of the phthalimido group), 1680 cm^{-1} (keto group), 1625 cm^{-1} (C=O of the β-lactam). The low solubility of the substance made it impossible to obtain its NMR spectrum. Found %: C 70.68; H 4.21; N 9.09. $C_{36}H_{24}N_4O_6$. Calc. %: C 71.05; H 3.94; N 9.21.

Hydrazinolysis of Phthalimido-β-lactams. A mixture of 8.4 g (0.02 mole) of powdered 1-phenyl-3-phthalimido-4-(1-methyl-3-indolyl)azetidin-2-one (XII) and 1.63 g (0.024 mole) of hydrazine hydrate in 400 ml of alcohol was refluxed for 3 h until a clear solution formed, and the solution was allowed to stand overnight. It was then evaporated to one third of its volume and filtered. The precipitate was washed twice with cooled alcohol (15-ml portions) to give 2 g of the phthaloylhydrazine. The alcohol solution was distilled to dryness in vacuo to give a viscous mass, which, after trituration with a small amount of water, gave 3.7 g of impure 3-amino-1-phenyl-4-(1-methyl-3-indolyl)azetidin-2-one (XIII). IR spectrum ($CHCl_3$): 3410 and 3350 cm^{-1} (NH2), 1750 cm^{-1} (C=O) of the β-lactam).

A solution of 2.91 g (0.01 mole) of amine XIII in 20 ml of methanol was mixed with a solution of 1.46 g (0.01 mole) of adipic acid in 15 ml of methanol, and the mixture was refluxed under low heat for 15 min. A precipitate of 1.9 g (26%) of the adipate (neutral salt) of amine XIII with mp 140-142 deg (dec., from methanol) formed after standing at room temperature. IR spectrum (KBr): 1760 cm^{-1} (C=O) of the β-lactam).

Tosyl chloride [0.38 g (0.002 mole)] was added with cooling to a solution of 0.58 g (0.002 mole) of the amine in 3 ml of dry pyridine. The resulting solution was allowed to stand at room temperature for 2 h, after which it was treated with excess ice water. The resulting viscous oil was triturated with 5 ml of alcohol and cooled. A precipitate soon formed and was recrystallized from aqueous acetone to give 0.2 g (22%) of tosylamide XIV with mp 175 deg. IR spectrum ($CHCl_3$): 3380 cm^{-1} (NH), 1755 cm^{-1} (C=O) of the β-lactam). NMR spectrum ($CDCl_3$): δ 2.26 (CH_3-C), 3.65 ($N-CH_3$), 4.56 (3-CH, J = 2.5 Hz), 5.08 (4-CH, J = 2.5 Hz).

4-Acyl Derivatives of 3-Phenyl-3,4,5,5-tetrahydro-β-carboline. The reaction of 3-(2-benzylideneaminoethyl)indole [17] (XV) with the acid chlorides was carried out at room temperature via method B. When

phthalimidoacetyl chloride was used, a mixture was obtained, from which cis-β-lactam XVI (9.3%) with mp 224-226 deg was isolated by fractional crystallization from benzene. IR spectrum ($CHCl_3$): 1720 cm^{-1} (C = O) of the phthalimido group), 1760-1780 cm^{-1} (C = O) of the β-lactam and phthalimido groups). NMR spectrum (dimethyl sulfoxide): δ 5.15 (4-CH), 5.45 (3-CH), J = 6 Hz.

XVIIa had mp 234 deg. IR spectrum ($CHCl_3$): 1720, 1780 cm^{-1} (C = O) of the phthalimido group), 1660 cm^{-1} (C = O of a tertiary amide), 3480 cm^{-1} (NH). Found %: C 74.37; H 4.97; N 9.74. $C_{27}H_{21}N_3O_3$. Calc.. %: C 74.48; H 4.82; N 9.65.

XVIIb was obtained in 41% yield and had mp 263-265 deg (from aqueous acetone). IR spectrum ($CHCl_3$): 1635 cm^{-1} (C = O) of a tertiary amide), 3480 cm^{-1} (NH). Found %: C 78.24; H 6.35; N 9.46. $C_{19}H_{18}NO_2$. Calc. %: C 78.62; H 6.20; N 9.65. The low solubility of XVIIa and b made it impossible to obtain their NMR spectra.

The authors sincerely thank K. F. Turchin for interpreting the NMR spectra.

LITERATURE CITED

1. T. Kikuchi and S. Vyeo, Tetrahedron Lett., 3473 (1965).
2. A. K. Bose, B. Anjaneyulu, S. K. Bhattacharya, and M.S. Manhas, Tetrahedron, 23, 4769 (1967); A. K. Bose, V. Sudarsanam, B. Anjameyulu, and M. S. Manhas, Tetrahedron, 25, 1191 (1969).
3. H. T. Clarke, G. R. Johnson, and R. Robinson, The Chemistry of Penicillin, Princeton University Press (1949).
4. Organic Reactions [Russian translation], Vol. 9, Inostr. Lit., Moscow (1959), p. 504.
5. G. C. Sheehan and K. R. Henery-Logan, J. Am. Chem. Soc., 79, 1262 (1957); 81, 3089, 5838 (1959).
6. A. K. Bose, G. Spiegelman, and M. S. Manhas, J. Am. Chem. Soc., 90, 4506 (1968); Chem. Commun., 321 (1968).
7. E. P. Abraham and G. G. F. Newton, Biochem. J., 79, 377 (1961).
8. R. B. Woodward, K. Heusler, G. Gosteli, P. Naefeli, W. Oppolzer, R. Ramage, S. Ranganathan, and H. Vorbrüggen, J. Am. Che. Soc., 88, 852 (1966).
9. J. C. Sheehan and J. J. Ryan, J. Am. Chem. Soc., 73, 1204 4367 (1951).
10. H. B. Kagan, J. J. Basselier, and J. L. Luche, Tetrahedron Lett., 941 (1964).
11. D. A. Johnson and D. Mania, Tetrahedron Lett., 267 (1969).
12. J. P. Clayton, J. H. C. Nayler, R. Southgate, and E. R. Stove, Chem. Commun., 129 (1969).
13. E. Shaw and D. W. Wooley, J. Biological Chem., 203, 979 (1953); L. E. Weller and H. M. Sell, J. Org. Chem., 23, 1776 (1958).
14. R. Majima and M. Kotake, Ber., 58, 2037 (1925).
15. Synthesis of Organic Preparations [Russian translation], Vol. 11, Inostr. Lit., Moscow (1961), p. 30.
16. V. M. Rodionov and T. K. Veselovskaya, Zh. Obshch. Khim., 22, 2202 (1950).
17. T. Hoshino and Y. Kotake, Ann., 516, 76 (1935).
18. V. G. Avramenko, Khim.-Farmats. Zh., No. 6, 15 (1970).