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A MODIFICATION OF THE PLÖCHL-ERLENMEYER REACTION. I. SYNTHESIS OF 2-PHENYL-4-DIPHENYLMETHYLENE-5(4H)-OXAZOLONE

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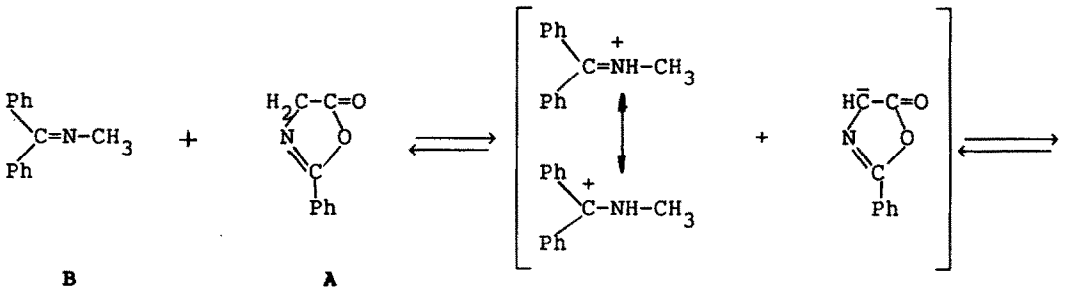
Abstract: *An N-methylketimine has been found to be an effective reagent in the Erlenmeyer azlactone synthesis. 2-Phenyl--4-diphenylmethylene-5(4H)-oxazolone* (**1**) *has been synthesized by the reaction of 2-phenyl-5(4H)-oxazolone* (**A**) *with N-methyl-diphenylmethanimine* (**B**), *contrary to previous attempts using benzophenone or its imines from aniline, benzylamine or n-butylamine. Quantitative reaction yield (UV-spectral determination) was achieved with A:B=3:1. Reaction conditions ensuring good yields of* **1** *are described. N-Methylhippuramide* (**3**), *N-methyl-2-(N-benzoylamino)-3,3-diphenylpropenamide* (**5**), *2-(N-benzoylamino)-3,3-diphenylpropenoic acid* (**7**) *and its ethyl ester* (**8**) *are also reported.*

The Plöchl-Erlenmeyer reaction, known as the Erlenmeyer azlactone synthesis, starting from acylated glycine derivatives and aldehydes or ketones, is a way to important intermediate products used in the synthesis of α-amino acids, peptides and related compounds[1-5]. Unsaturated azlactones and some of their derivatives are also of interest as anti-tumor agents[6]. The reaction is known to be applicable practically to aromatic aldehydes and a few ketones[1,5,7b,8-10]. Recently a modification of the Erlenmeyer reaction has been developed using the imines of the carbonyl compounds, obtained with aniline[7], benzylamine[11] or n-butylamine[12]. However, the imines of benzophenone and benzil failed to react[12].

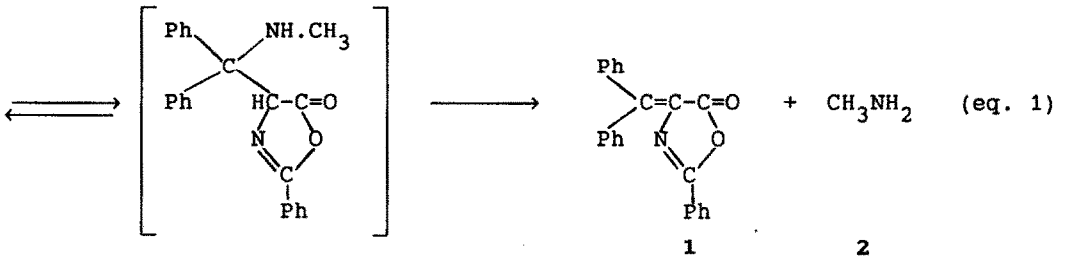
Herein is reported that the N-methylimine of benzophenone (**B**) reacts with 2-phenyl-5(4H)-oxazolone (**A**, generated from hippuric acid), to give the corresponding unsaturated azlactone (**1**).

On the basis of the components isolated from the reaction mixture and considering literature data[5,7,11-13] we assume that the reaction proceeds according to eq. 1. The reaction mixtures always contain

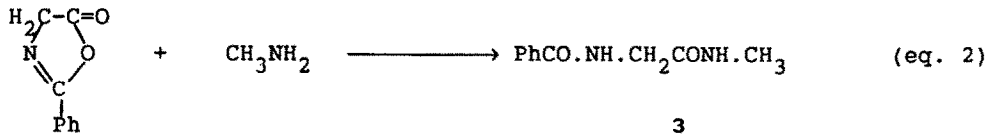
N-methylhippuramide (**3**), the product of the action of the evolving methylamine (**2**) on unreacted 2-phenyl-5(4H)-oxazolone (**A**, eq 2). The above processes take place even at room temperature. Under the chosen reaction conditions (benzene solvent, no additional condensing agent, 50-55°C, 1 hour), the reaction corresponding to eq.1 is fast, the main quantity of **2** evolves and only small amounts of side products appear, mainly N-methylhippuramide (**3**). During the isolation of the main product (**1**), hippuric acid (**4**) is also formed (eq.3). N-Methyl-2--(N-benzoylamino)-3,3-diphenylpropenamide (**5**, eq.4) was found in reaction mixtures which had been heated for a longer time (for instance more than 2 hours at 50-55°C) or had been kept (in solution or without solvent) at room temperature for more than 12 hours. There was no evidence for the formation of ß-lactams (**6**, eq. 5), unlike the reaction of benzylidene-methylamine with 2-phenyl-4-methyl-5(4H)-oxazolone[14].



B **A**



1 **2**



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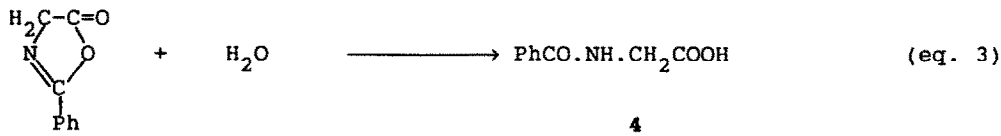

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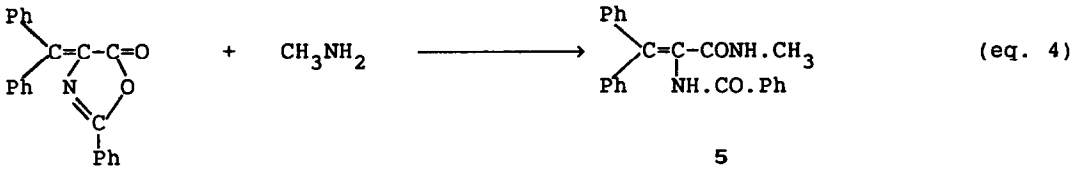
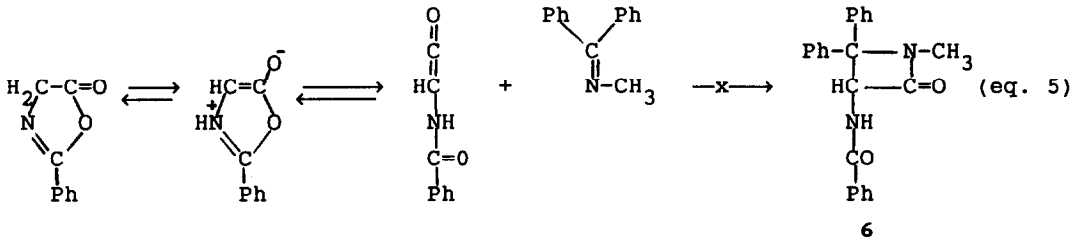


(eq. 4)

5



(eq. 5)

6

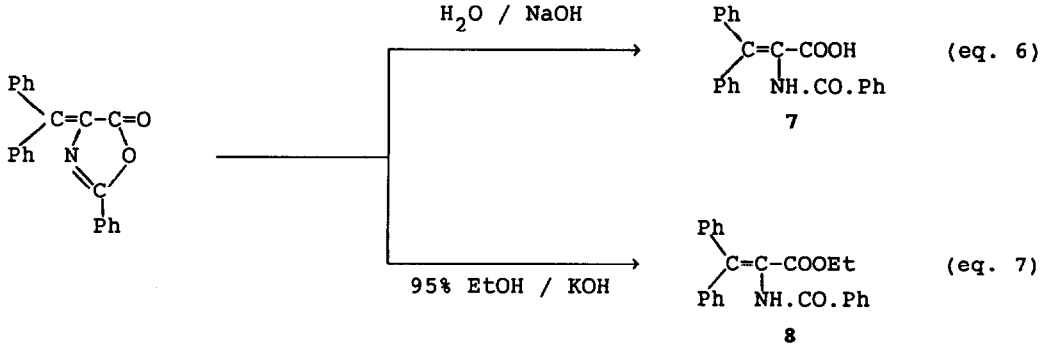
It has been known[8a], that higher yields are obtained with the Erlenmeyer reaction, if any of the reagents is taken in excess. The common use is to take the carbonyl component in excess[8-10]. Kumar et al[7b] have prepared unsaturated azlactones from hippuric acid, triethylamine and ethyl chloroformate, taking 1,2 mole of each per mole of the imine.In the present work, preparative experiments for the synthesis of **1** with equimolar amounts of **A** and **B** have been carried out with **A**, obtained by two different ways: a) as a solid substance[15]or b) in benzene solution[7b,16], taking equimolar (to the imine) quantities of hippuric acid, triethylamine and ethyl chloroformate. As the yields were about the same (31-34%), it was assumed that the chosen (b) experimental conditions ensure quantitative (or near to it) transformation of hippuric acid into **A**. Further in this work in the case of b), molar ratio **A:B** will imply the molar quantity of hippuric acid, triethylamine and ethyl chloroformate per mole of the imine (**B**).

To find out conditions for higher yields of **1**, quantitative experiments with UV-spectral determination of the product were carried out under variable synthetic conditions: presence or absence of condensing agent (triethylamine), molar ratio **A/B**, duration or order of mixing. Some of the results are collected in the Table. Similarly to the known modification[7], reaction (eq.1) proceeds in the absence of a condensing agent (triethylamine). But with lower reagent concentration (2-3 $x10^{-3}$ mol/l), catalytic amounts of triethylamine (0.2 mole per mole of the reagents) accelerate the reaction[17]. An increase of the yield of **1** is

observed only in case of taking reagent **A** in excess, and the effect is considerable. Thus, with 2 mole of **A** per mole of **B**, the yield of **1** increases more than twice, and it becomes quantitative with **A:B**=3:1. The order of mixing also affects, though weakly, the reaction yield. With equimolar amounts of **A** and **B**, a higher yield is obtained, when the solution of the imine is added to that of **A**, opposite to the common practice[7].

The product, 2-phenyl-4-diphenylmethylene-5(4H)-oxazolone, may be kept for 24 hours in alcohol at room temperature or boiled in it for recrystallisation without alcoholysis occuring.

The aminolysis products of **A** and **1**, N-methylhippuramide (**3**, eq.2) and N-methyl-2-(N-benzoylamino)-3,3-diphenylpropenamide (5, eq.4) respectively, have been isolated, identified and high yield procedures for their preparation have been described. Through alkali catalyzed hydrolysis (eq.6) and alcoholysis of **1** (eq.7), 2-(N-benzoylamino)--3,3-diphenylpropenoic acid (7) and its ethyl ester (8) have been obtained.



(eq. 6)

(eq. 7)

In conclusion, the reaction of 2-phenyl-5(4H)-oxazolone with the N-methylimine of benzophenone (a sterically hindered ketone, which is inert under the conditions of the classical Erlenmeyer reaction, as in the case of other imines of it[12]) is a convenient method for the synthesis of 2-phenyl-4-diphenylmethylene-5(4H)-oxazolone, which has not been accessible in another way. The preparative yield is more than 30%, starting from an equimolar mixture of the reagents and more than 75% if an excess of 2-phenyl-5(4H)-oxazolone is used (2 moles/ 1 mole imine). It is to be expected that some carbonyl compounds, which have been found inert in the Erlenmeyer reaction (including its imine modification[5,7,12]), could react through their N-methylimine derivatives.

EXPERIMENTAL

Melting points were determined on a Boetius PHMK apparatus and are uncorrected. NMR spectra were recorded on a Bruker WM 250 (250 MHz) and chemical shifts are reported as δ values relative to $(CH_3)_4Si$ as internal standard. Mass spectra were obtained on a MS JEOL JMS-D 300 spectrometer (electron impact 70 eV). IR spectra were recorded on Bruker IFS 113v. UV spectra were measured with a Specord UV-vis instrument, Carl Zeiss Jena. The solvents used were of spectroscopic grade; stock solutions of the compounds in EtOH or $CHCl_3$ were prepared immediately before use. Analytical thin-layer chromatography (TLC) was carried out on Merck precoated silica gel F-254 plates (thickness 0.2 mm). Spots were visualized with an UV lamp (254 nm). Purification of the products achieved by recrystallisation. All solvents were dried. All amines, ethyl chloroformate and inorganic reagents were chemically pure and used without purification. Hippuric acid was purified by recrystallization (water). 2-Phenyl-5(4H)-oxazolone was prepared by cyclodehydration of hippuric acid and was either a) isolated and stored as a solid substance[15] or b) used freshly prepared as a benzene solution[7b,16]. The powder product[15] remained unchanged for months in a desiccator. N-Methyl-diphenylmethanimine was obtained starting from benzophenone[18a], though an older procedure can be successfully used[18b]. Its purity (for carbonyl group) was controlled by IR. The reagents and the reaction mixtures were preserved from humidity.

Determination of the Reaction Yield of 2-Phenyl-4-(Diphenyl)methylene-5(4H)-Oxazolone (1).

Table represents the results of UV-determination of reaction yield of **1** ($CHCl_3$, 373.3 nm) as obtained at 50-55°C in dry benzene in the presence of catalytic amounts of Et_3N (0.2 mole per 1 mole hippuric acid, resp. **A**). The concentrations given in the Table refer either to both reagents (when taken in equimolar quantities) or to that one taken in lower quantity. Preliminary experiments[17] in the conditions described in the Table with equimolar **A/B** and duration 1 hour showed, that with the concentrations used in this type of experiments, the above Et_3N amount accelerates the reaction (eq.1). In the preparative experiments however the same Et_3N quantities have no effect. 2-Phenyl-5(4H)-oxazolone (2.5 mmol) was prepared from hippuric acid (448 mg, 2.5 mmol), Et_3N (d_4^{20} 0.72, 430 μl, 3 mmol) and ethyl chloroformate (d_4^{20} 1.139, 243 μl, 2.5 mmol) as a benzene solution before the experiment as will be described with the preparative experiments (IIa). The benzene solution was transferred in a 25 ml measuring flask and diluted to the mark. Aliquot samples, containing the

necessary quantities of **A**, were taken with pipettes from this solution. Further the procedure was analogous to that used in the preparative experiments except for the much smaller quantities: To a benzene solution of **A**, maintained at 50-55°C, a benzene solution of **B**, (3 ml) was added dropwise over 10 min. The mixture was stirred for the time given in the Table (reaction time). The dry residue, obtained under reduced pressure (Rotavapor) at close to room temperature, was dissolved in dry $CHCl_3$ and quantitatively transferred into a 25 ml measuring flask. The absorbance of an aliquot sample of this solution diluted in $CHCl_3$ was measured (λ 373.3 nm) and the reaction yield was determined using a calibration curve.

Table Reaction yield of **1**, obtained at 50-55° C in benzene

ENTRY	REACTION CONDITIONS						Reaction yield
	REACTANTS			Reaction time	Volume of solvent	Concentration x10^{-2}	
	B	**A**	Mol.ratio **B:A**				
	[mmol]	[mmol]	-	[h]	[ml]	[mol/l]	[%]
1	0.200	0.200	1:1	1	7	2.86	44.8
2*	0.200	0.200	1:1	2	7	2.86	44.6
3*	0.200	0.200	1:1	1	7	2.86	42.0
4	0.600	0.200	3:1	1	7	2.86	41.7
5	0.203	0.400	1:1.97	1	7	2.90	91.0
6	0.200	0.400	1:2	1	7	2.86	95.8
7	0.200	0.600	1:3	1	8	2.50	100.0

*In this experiment the solution of **B** was added to the solution of **A**.

2-Phenyl-4-Diphenylmethylene-5(4H)-Oxazolone(1).

I. Using **A**, *prepared as a solid substance*[15]

a/ Molar ratio A:B=1:1

To a stirred suspension of **A** (161 mg, 1 mmol) in benzene (7 ml), maintained at 50-55°C (oil bath), a solution of **B** (195 mg, 1 mmol) in benzene (2 ml) was added dropwise over 15 min. The reaction mixture was stirred for 1 hr at the same temperature. The solvent was then removed by rotary evaporation, (t < 50°C) and the solid residue was suspended in EtOH (3-5 ml). After filtration, the solid product was recrystallized in ethanol to give fine yellow needles, mp 186.5-187.5°C (111 mg, 34%). IR ($CHCl_3$) [cm^{-1}]: 1794(s), 1766(m), 1632(s), 1600(w), 1575(w), 1540(w), 1451(m), 1444(m), 1329(m), 1322(m), 1220(m), 1176(w), 1038(m), 998(m), 888(m), 661(m), 571(w). UV (EtOH) λ [nm]; ε [l/(mol.cm)]: λ 206 (ε 32200),

λ 223 (ε 11200), λ 260 (ε 18900), λ 370.4 (ε 27600); UV ($CHCl_3$): λ 264 (ε 19000), λ 373.3 (ε 27500). ^{13}C NMR ($CDCl_3$): 165.5 (s, C=O), 162.2 (s, C=N), 150.4 (s, C_4), 138.6, 136.9 and 125.9[19] (each s, C_5, C_6, $C_{6'}$ and C_7), 133.0-127.5 (each d, CH_{arom}). MS m/e: 325 (M^+, 30), 105(100), 77 (40).

b/ Molar ratio A:B=2:1

Under the conditions and by the procedure above described, **A** (322 mg, 2 mmol) in benzene (3 ml) and **B** (100% C=N-, 195 mg, 1 mmol) in benzene (2 ml) produced after fractional recrystallization (EtOH) **1** (253 mg, 78%)

II. Using A, freshly prepared in benzene[7b,16]

a/Molar ratio A:B=1:1

Reagent **A** was prepared[7b,16] as follows: to a well stirred suspension of hippuric acid (1255 mg, 7 mmol) and Et_3N (d_4^{20} 0.720; 1005 μl, 7 mmol) in benzene (8 ml), a solution of ethyl chloroformate (d_4^{20}1.139; 681 μl, 7 mmol) in benzene (4 ml) was added dropwise over 20 min at RT. The funnel was washed with benzene (4 ml) and the mixture was stirred at RT for 4 hr. The white residue was filtered off by suction and washed with small benzene portions (10 ml in all). The filtrates were collected in a two-necked flask.

To above solution of **A** in benzene (26 ml), maintained at 50-55°C a solution of **B** (1368 mg, 7 mmol) in benzene (4 ml) was added dropwise over 15 min. Stirring was going on for 1hr, after which benzene was removed under reduced pressure. The pasty residue was treated as described (Ia) to give **1**, 730 mg, 32%.

b/ Molar raio A:B=2:1

Following the above described procedure, a solution of **A** (14 mmol) [obtained from h.a. (2510 mg, 14 mmol), t.e.a.(d_4^{20} 0.720; 2010 μl, 14 mmol) and e.c.f. (d_4^{20} 1.139; 1363 μl, 14 mmol)] in benzene (42 ml) was brought in reaction with **B** (1368 mg, 7 mmol) to produce a raw product, which was submitted to fractional recrystallization to give **1** in an overall yield of 1730 mg (76%).

c/ Molar ratio A:B=2:1 in the presence of Et_3N

In the conditions of IIb, when the solution of **A** contained Et_3N (0. mole/ 1 mole **A**), the yield of **1** was 1706 mg (75%).

N-Methylhippuramide (3).

To the joint solutions of **A** in benzene (45 ml), obtained as described in IIa, starting with 10 mmol hippuric acid, a solution of CH_3NH_2 (33% in abs. EtOH, d_4^{20} 0.756; 1.245 ml, 10 mmol) in benzene (10 ml) was added gradually under stirring at RT. The stirring went on for 1 h. The mixture was filtered and the white residue was recrystallized in ethanol. Yield 1392 mg (72%), a white powder, mp 161.0-161.5°C. MS m/e: 193 (M+1, 1.0), 162 (1.0), 135 (84.0), 105 (100), 77 (58.0), 58 (13.0), 51 (18.0). UV (EtOH): 205 nm (ε 14200), 228 nm (ε 14400). IR (KBr): 3296 (m), 3089-3072 (w), 1674 (s), 1642 (s), 1605 (m), 1552 (s), 1491 (w), 1446 (m), 1340 (w), 1250 (w), 1169 (w), 712 (w), 690 (m). ^{1}H-NMR (DMSO-d_6) δ [ppm]: 2.60 (d, J=4.52 Hz, 3H, CH_3), 3.83 (d, J=5.90 Hz, 2H, CH_2), 7.91-7.44 (m, 6H, C_6H_5 and CO.N<u>H</u>.CH_3), 8.75 (t, J=5,66 Hz, 1H, PhCO.N<u>H</u>).

N-Methyl-2-(N-Benzoylamino)-3,3-Diphenylpropenamide (5)

A well stirred gradually thickening suspension of **1** (325 mg, 1 mmol) and methylamine (33% in abs. EtOH, d_4^{20} 0.756; 125 μl, 1mmol) in ethanol (5ml) was gradually diluted with ethanol (15 ml) at RT over 15 min. The mixture was stirred for 2 hours at room temperature and was filtered off. The crude white solid product was recrystallized from ethanol to give a white product **5** (335 mg, 94%) m.p. 253-255°C. MS: m/e 356 (M, 18) 325 (2.0), 193 (12.0), 165 (16.0), 105 (100), 77 (37.0), 51 (2.0). UV (EtOH): 205 nm (ε 39000), 232 (ε 28900), 300 nm (e 14600). IR (KBr) [cm^{-1}]: 3315 (m), 3261 (m), 1648 (s), 1641(s), 1614 (w), 1537(m), 1522 (m), 1480)m), 1444(w), 1296 (m), 1261 (w), 1097 (w), 1076 (w), 806 (w), 769 (w), 694 (w). ^{1}H-NMR (DMSO-d_6) δ [ppm]: 2.37 (d, J=4.50 Hz, 3H, CH_3), 7.78-7.07 (m, 16H, 15_{arom}+CO.N<u>H</u>.CH_3), 9.71 (s, 1H, PhCO.N<u>H</u>, exchangeable).

2-(N-Benzoylamino)-3,3-Diphenylpropenoic Acid (7)

1 (325 mg, 1 mmol) was suspended in 1% water solution of NaOH (25 ml) and vigorously refluxed till complete dissolution. The flask was cooled and the solution was sloowly acidified with 3 M HCl. The white resudue was washed with water on the filter and dried. Crystallization in ethanol-water (the solution was cooled overnight) afforded **7** as white crystals (306 mg, 88%), m.p. 212-214°C; UV (EtOH): 204 nm (ε 39600), 232 nm (ε 23900), 300 nm (ε 14200). IR (KBr) [cm^{-1}]: 3245 (m), 3030 (m), 1716 (s), 1624 (m), 1576 (w), 1522 (m), 1350 (s), 1311 (m), 1207 (w), 1159 (w), 773 (w), 731 (m), 679 (w), 536 (w). ^{1}H NMR (DMSO-d_6), δ [ppm]: 7.82-7.09 (m, 15H, arom.), 9.97 (s, 1H, N<u>H</u>, exchangeable), 12.08 (s, 1H, COOH, exchangeable). MS, m/e; 343 (M^+, 4.0), 299 (20.0), 193 (16.0), 165 (20.0), 105 (100), 77 (62.0), 51 (10,0).

Ethyl-2-(N-Benxoylamino)-3,3-Diphenylpropenoate (8)

A suspension of **1** (977 mg, 3 mmol) and KOH (0.9 ml 0,18M ethanol solution) in 95% ethanol (90 ml) was refluxed until the azlactone (1) was disappeared . The solution was concentrated in vacuum, the concentrate was cooled and diluted with water (~ 200 ml). The precipitate was filtered off, washed with wat er on the filter and recrystallized from ethanol to give white product **8** (683 mg, 61%, m.p. 149.0-149.5^{o}C) MS, m/e: 371 (M^{+}, 56.0), 193 (12.0), 165 (18.0), 105 (100.0), 77 (42.0), 51 (2.0). UV (EtOH): 207 nm (ε 32000), 232 nm (ε 24800), 303 nm (ε 15700). IR (KBr) [cm^{-1}]: 3313 (m), 1705 (s), 1668 (s), 1510 (m), 1483 (m), 1390 (m), 1309 (m), 1207 (m), 1020 (w), 744 (w), 702 (m), 546 (w); ^{1}H-NMR (DMSO-d_6) δ [ppm]: 0.78 (t, J=7.10 Hz, 3H, CH_3), 3.85 (q, J=7.08 Hz, 2H, CH_2), 7.83-7.05 (m, 15H, arom), 10.09 (s, 1H, NH, exchangeable).

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REFERENCES

1. Carter, H.E., In *Org. React.*, Adams, R. Ed.; John Wiley and Sons, Inc.:New York, **1946**, 3, 198-239.
2. Greenstein, J.P. and Winitz, M.,"*Chemistry of Amino Acids*", John Wiley & Sons, Inc.: New York, **1961**, pp 706 and 823-843.
3. Vineyard, B.D., Knowles, W.S., Sabacky, M.J., Bachman, G.L. and Weinkauff, D.J., *J.Am.Chem.Soc.*, **1977**, 99, 5946-5952.
4. Filler, R. and Rao, Y.S., In *Adv. Heterocycl. Chem.*, Katritzky, A.R. and Boulton, A.Y. Eds.; Academic Press, Inc.: New Uork, **1977**, 21, 175-206.
5. Mukerjee, A.K., *Heterocycles*, **1987**, 26, 1077-1097.
6. a/ Boltze, K.H., Etschenberg, E., Opitz, W., Radatz, S., Wellbrecht, D., *German Patent* 2,659, 543 (**1978**); C.A. 1978, 89, 179979;
b/ Etschenberg,E., Opitz, W., Radatz, S., *German Patent* 2, 659, 114 **(1978)**, C.A. 1979, 90, 55277;
c/ Etschenberg, E.,Opitz, W., Radatz,S., *German Patent* 2, 745, 584 **(1979)**, C.A. 1979, 91, 74907;

d/ *German Patent* 2904512 **(1980)** C.A. 1981, 94, 47753;

e/ *U.S. Patent* 4310517 **(1982)**; C.A. 1982, 97, 72781.

7. a/ Rai, M., Krishan, K., Singh, A., *Indian J. Chem.*, **1977**, 15B, (9), 847-848.

b/ Kumar, P., Mishra, H.D., Mukerjee, A.K. *Synthesis*, **1980**, (10), 836-839.

c/ Kumar, P., Mukerjee, A.K. *Indian J. Chem.*, **1981**, 20B, (5), 418-419.

8. a/ Crawford, M., Little, W.T., *J. Chem.Soc.*, **1959**, 729-731.

b/ Cativiela, C., Melendez, E., *Synthesis*, **1978**, (11), 832-834.

9. Ramage, G.R.and Simonsen, J.L., *J. Chem. Soc.*, **1935**, 532.

10. *The Chemistry of Penicillin*, Ed. Clarke, H.T., Johnson, J.R.& Robinson, R., Princeton University Press, Princeton, **1949**, pp 783, 792.

11. Kumar, S., Rai, M., Krishan, K., Singh, A., *J. Indian Chem. Soc.*, **1979**, 56, (4), 432-433.

12. Mukerjee, A.K and Kumar, P., *Heterocycles*, **1981**, 16, (11), pp. 1995-2034, 2004.

13. Singh, N and Sandhu, J.S., *J. Indian Chem. Soc.*, **1969**, 46, (8), 751-753.

14. Huisgen, R., *Aromaticity*, Chem. Soc., Special publication No 21, **1967**, p. 51-73.

15. Hoyng, C.H., McKenna, M.G., Walters, D.L., *Synthesis*, **1982**, (3), 191-192.

16. Kumar, P., Mukerjee, A.K., *Synthesis*, **1979**, (9), 726-727.

17. Ivanova, G.G., unpublished results.

18. a/ Duffaut, N. and Dupin, J.P., *Bull. Soc. Chim. Fr.*, **1966**, (10), 3205-3210; b/ Reddelien, G., *Ber.*, **1921**, 54, 3130.

19. Prokof'ev, E.P., Karpeiskaja, E.I., Chel'tsova, G.V., Dantsig, T.B., *Izv. Akad. Nauk SSSR, Ser Khim.* **1980**, (4), 823-829.