REACTION OF DIPHENYLCYCLOPROPENONE WITH 2-AMINOTHIAZOLES AND RELATED COMPOUNDS

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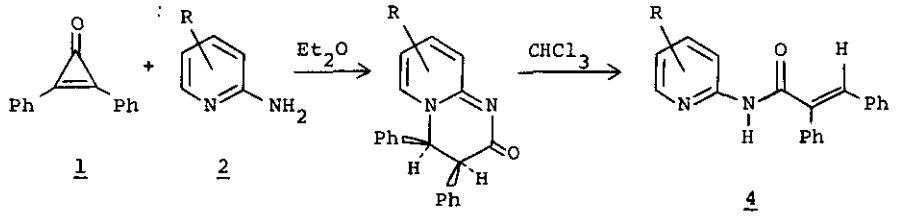
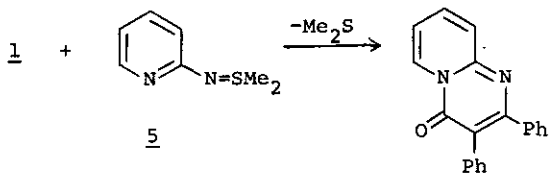
Abstract — Diphenylcyclopropenone (1) reacts readily with 2-aminothiazole (7a) in THF to produce cis-5,6-dihydro-5,6-diphenyl-7H-thiazolo[3,2-a]pyrimidin-7-one (8a) in high yield. 2-Amino-5-ethyl-1,3,4-thiadiazole (7b) and 2-aminothiazoline (7c) react similarly, while 2-amino-4-methylthiazole (7d) affords both 8d and the cis-2,3-diphenylacrylamide 11. 2-Amino-4-ethyl-5-methylthiazole (7e) and 2-aminobenzothiazole (7f) give no 8, the products isolated being the corresponding cis-2,3-diphenylacrylamides 12 and 13. 2-Aminobenzimidazole (16a) yields 17a and 17b, while 2-amino-5-chlorobenzimidazole (16b) produces 18a, 18b, and 19.

Some time ago, we reported[1] the formation of cis-3,4-dihydro-3,4-diphenyl-2H-pyrido[1,2-a]pyrimidin-2-ones 3 as minor products from the reaction of diphenylcyclopropenone (1) with a variety of 2-aminopyridines 2. Transformation of 3 to 4, the major product isolated in the reaction, occurred readily in chloroform



1 2 3 4

solution at room temperature. More recently, compounds analogous to 3 have been observed[2] in reactions of 1 with amidines and guanidines. Among the factors contributing to the facility of the ring-opening process in 3, one might cite an unfavorable H-6: phenyl interaction and the tendency towards the benzenoid-like aromatic nucleus in 4. With the objective of evaluating the potential of the above reaction in the synthesis of bicyclic systems, a study of the reactivity of 1 with 2-aminothiazoles and related compounds was undertaken. Furthermore, since the reaction of 1 with sulfimide 5 has been reported[3] to yield the pyrimidin-4-one 6, the obtention of stable analogs of 3 in high yields would suggest a promising role for the aminoheterocycle-sulfimide derivative combination in the synthesis of certain isomeric annelated pyrimidones.



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RESULTS AND DISCUSSION

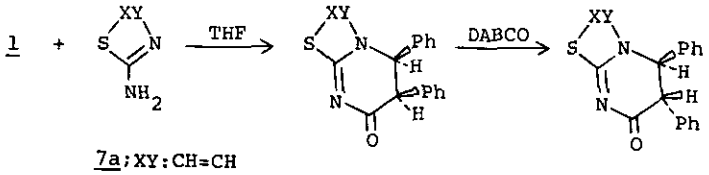
Diphenylcyclopropenone (1) reacted smoothly with 2-aminothiazole (7a) and 2-amino-5-ethyl-1,3,4-thiadiazole (7b) in tetrahydrofuran at room temperature. The reaction of 1 with 2-aminothiazoline (7c) was rapid and exothermic. In each case, an ether insoluble, crystalline solid was isolated in high yield (see Table I). This

Table I

Formation of pyrimidones 8 and/or cis-2,3-diphenylacrylamides (11-13) from cyclopropenone 1 and 2-aminoheterocycle 7 in THF.

Aminoheterocycle	Reaction time, days	Product (% Yield)
7a	3	8a (85%)
7b	6	8b (90%)
7c	1	8c (95%)
7d	20	8d (34%)
		11 (54%)
7e	30	12 (45%)
7f	30	13 (80%)

material was a 1:1 adduct as indicated by elemental analysis, mass spectra, and nmr integration. The nmr spectra contained a pair of doublets with coupling constant and chemical shifts similar to those of H-3 and H-4 of 3. The ir spectra (KBr) showed a single intense absorption in the 1600-1800 cm^{-1} region (1650-1670 cm^{-1}).



7a; XY: CH=CH
b; XY: CEt=N
c; XY: CH_2CH_2
d; XY: CH=CMe

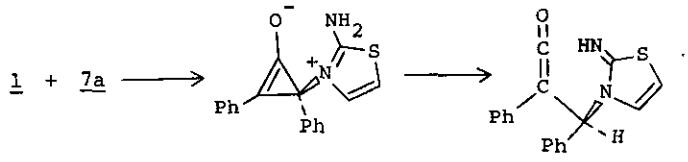
8 9

The assignment of 7-one structure 8 to these products was based upon a comparison of the ir spectral characteristics with those of some model compounds. Thus, the reaction of 7a with methyl acrylate has been reported to give 5,6-dihydro-7H-thiazolo|3,2-a|pyrimidin-7-one,[4] which shows a single intense absorption at 1630 cm^{-1}. 5,6-Dihydro-7H-benzothiazolo|3,2-a|pyrimidin-7-one shows absorption at 1653 cm^{-1}.[5] In contrast, the 5-one systems characteristically present distinct carbonyl and imine absorptions above 1600 cm^{-1}. For example, a 6,7-dihydro-5H-benzothiazolo|3,2-a|pyrimidin-5-one has been reported to show absorptions at 1714 (C=O) and 1648 (C=N) cm^{-1},[6] a 6,7-dihydro-5H-1,3,4-thiadiazolo|3,2-a|pyrimidin-5-one at 1727 (C=O) and 1638 (C=N) cm^{-1},[6] and 2,3,6,7-tetrahydro-5H-thiazolo|3,2-a|pyrimidin-5-one at 1686 (C=O) and 1640 (C=N) cm^{-1}.[7] We have observed the formation of the 7-one isomer of this latter compound from the reaction of 7c with methyl acrylate. The ir spectrum of this material showed a single intense absorption at 1660 cm^{-1}. The formation of 8b from the reaction of 1 with 7b apparently represents the first report of this system. Attempts at preparing the parent compound from 7b and methyl acrylate were unsuccessful.

In comparison with 3, 8a, 8b, and 8c demonstrated a remarkable stability in solution. The nmr spectra of samples which had remained in the nmr tube for 10 days showed no evidence of transformation. However, a slow, quantitative conversion to the trans isomers 9 was observed in acetone containing DABCO.

The formation of 8 may be visualized as occurring by way of a highly stereo-

specific and efficient intramolecular interception of a ketene intermediate, 10, formed by initial conjugate addition of the ring nitrogen of 7 on the electrophilic cyclopropenone ring. For the reaction of 2-aminopyridines 2, an analogous intermediate was proposed to account for the formation of both 3 and cis-2,3-diphenylacrylamides 4, in view of the observed lack of reactivity of aniline. 2-Amino-6-methylpyridine reacted very slowly, eventually affording only the



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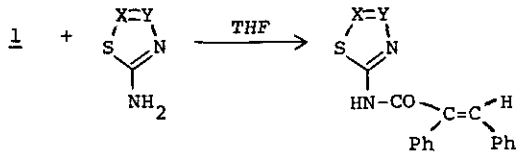
corresponding 4. The failure of 6-substituted 2-aminopyridines to form cyclic derivatives by reaction at the ring nitrogen had been observed previously, and had been attributed to steric hindrance.[8] With the objective of determining the steric situation necessary to encourage such a process in 7a, a study of several 4-substituted 2-aminothiazoles was performed.

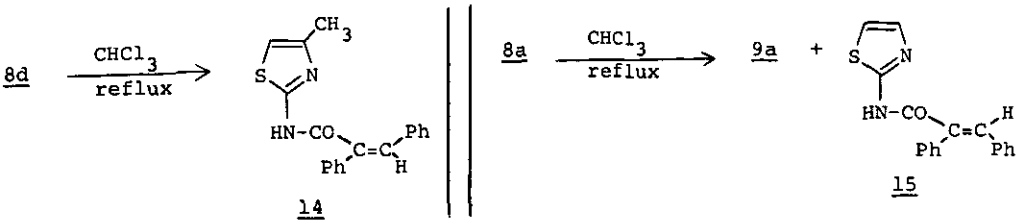
2-Amino-4-methylthiazole (7d) reacted slowly with 1 to give the ether insoluble 8d in 34% yield. From the ether soluble part, a 1:1 adduct (54%) was isolated which was assigned the cis-2,3-diphenylacrylamide structure 11 based upon the appearance in the nmr spectrum of a sharp 1H olefinic absorption at $\delta 8.0$[1] and absorptions at 3378 and 1666 cm^{-1} in the ir spectrum ($CHCl_3$). 2-Amino-4-ethyl-5-methylthiazole (7e) and 2-aminobenzothiazole (7f) gave no 8, the products isolated being the corresponding 12 and 13. The failure of 7f to form a cyclic derivative may be attributed to both steric and electronic factors, the



7d; X=CH, Y=CMe — 11
e; X=CMe, Y=CEt — 12
f; XY=C_6H_4 — 13

rearrangement of an intermediate such as 10 being dependent on the efficiency of the thiazole ring nitrogen as a leaving group. In methanol containing DABCO, 8d

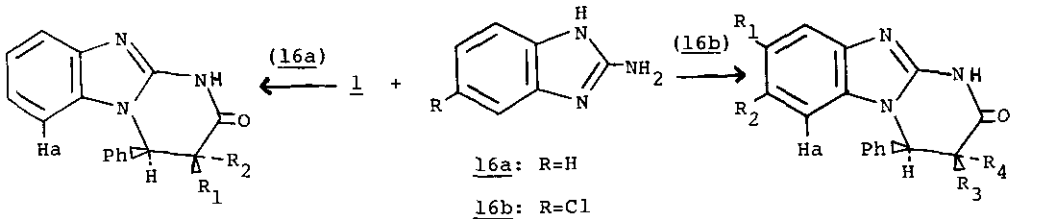
slowly isomerized to 9d, while in refluxing chloroform a slow transformation to 14 (80% based upon unrecovered 8d) was observed. The structure assignment of 14 was suggested by the similarity of the ir spectrum to that of 11 and the presence in the nmr spectrum of a sharp 1H olefinic absorption at δ6.95 (the olefinic hydrogen of trans-2,3-diphenylacrylic acid appears at δ6.95). Neither 9d nor 11 was transformed to 14 under reflux conditions in chloroform, suggesting that 14



arises directly from 8d. Under these same conditions, 8a was transformed at a faster rate to a mixture of 9a (73%) and 15 (12% , whose nmr spectrum showed the characteristic olefinic absorption at δ8.0). The formation of 15 from 8a parallels that of 4 from 3 and may be explained in a similar fashion, that is, by considering a conformation of 8a wherein the C_6H and C_5N bonds are in an anti-periplanar arrangement to facilitate a concerted olefin-forming elimination process. In fact, due to the cyclohexane-like nature of C_5 and C_6, such an arrangement requires that the C_5 phenyl occupy an equatorial position. We suggest that such a conformation is disfavored in 8d owing to an unfavorable Me-Ph interaction, and that in this case ring opening occurs through a non-concerted pathway involving a transition state in which the bulky phenyl groups move away from each other.

In contrast to the behavior of 7f with 1, where only the cis-2,3-diphenylacrylamide 13 was obtained, reaction of 2-aminobenzimidazole (16a) under the above conditions proceeded much more rapidly (complete reaction after 1 day) to afford both cis- and trans-dihydropyrimidinones 17a (38%) and 17b (30%), respectively. The nmr spectrum (CF_3CO_2H) of 17b contained two 1H doublets with J = 11 Hz, suggesting an appreciable contribution from a conformation with equatorial phenyls. Perhaps as a result, Ha appeared at δ6.4.

In as much as one route to 17b would involve cyclization of a 2,3-diphenylacrylamide analog of 13 (the other route being isomerization of 17a), a study of the reactivity of the unsymmetrical 2-amino-5-chlorobenzimidazole (16b) was undertaken. In this case, 18a (12%), 18b (10%), and 19 (50%) were isolated. The



17a: R_1=Ph;R_2=H

17b: R_1=H;R_2=Ph

16a: R=H

16b: R=Cl

18a: R_1=R_4=H;R_2=Cl;R_3=Ph

18b: R_1=R_3=H;R_2=Cl;R_4=Ph

19: R_1=Cl;R_2=R_3=H;R_4=Ph

nmr spectrum (CF_3CO_2H) of 18b contained a broadened 1H singlet at δ6.35 for Ha, while that of 19 contained a doublet (J = 9 Hz) at δ6.25. Isomerization of 18a to 18b was observed in CF_3CO_2H and in DMF (110°C). The fact that the major product from the reaction, 19, is isomeric with 18b favors a route to the trans-dihydropyrimidinones involving the intermediacy of 2,3-diphenylacrylamides. The lower yield of 18a as compared to 17a may be attributed to a stereo-electronic effect of chlorine, making the benzimidazole nucleus a better leaving group upon cyclization of an intermediate analogous to 10. The obtention of only one cis-diphenyl isomer (18a) here is consistent with representation of 16b in the tautomeric form shown, wherein the nucleophilicity of N-3 should predominate in the formation of a kinetic product.

The results of the present study demonstrate the role of steric and electronic factors in the reaction of 1 with 2-aminoheterocycles, a process which emphasizes once again the continuing utility of cyclopropenones in the synthesis of a wide variety of heterocyclic systems.

EXPERIMENTAL SECTION[9]

General Procedure

Reaction of Diphenylcyclopropenone (1) with 2-Aminoheterocycles 7 - The selected aminoheterocycle 7 (2 mmol) was added to a solution of diphenylcyclopropenone (0.412 g, 2 mmol) in 5 ml of dry THF. A solution was formed in all cases except that of 7b. An instantaneous, exothermic reaction was observed for 7c, with a white solid mass forming after several minutes. For 7a, 7b, and 7d, a crystalline solid was observed after 2 days. After the determined time, the solvent was separated from the precipitated solid 8 from 7a-d. Evaporation of the solvent and treatment of the residue in these cases with ether afforded more 8. The total yields of 8 are reported in Table I. Treatment of the residue from 7f with ether gave insoluble 13. When the ether soluble part of 7d and the crude

Some cis-Dihydropyrimidones (8)

Compound	mp °C	Formula		Anal. Data C	H	N	S	Nmr Data ($CDCl_3$)δ	IR Data (KBr)cm^{-1}	UV Data λ_{max}^{EtOH} (ε)
8a	167-170	$C_{18}H_{14}N_2OS$	Calcd	70.56	4.61	9.14	10.47	4.25(1H,d,J=7Hz)	1650	307(16,300)
			Found	70.44	4.58	9.02	10.38	5.40(1H,d,J=7Hz)	1480	
								6.50(1H,d,J=5Hz)	1455	
								6.65-7.40(11H,m)		
8b	180-183	$C_{19}H_{17}N_3OS$	Calcd	68.04	5.11	12.54	9.56	1.25(3H,t,J=7Hz)	1655	292(16,300)
			Found	67.89	5.14	12.43	9.60	2.75(2H,q,J=7Hz)	1485	
								4.45(1H,d,J=7Hz)	1455	
								5.50(1H,d,J=7Hz)		
								6.60-7.30(10H,m)		
8c	190	$C_{18}H_{16}N_2OS$	Calcd	70.10	5.23	9.08	10.40	3.00-4.00(4H,m)	1672	251(17,800)
			Found	69.89	5.15	8.98	10.54	4.26(1H,d,J=7Hz)	1533	
								4.77(1H,d,J=7Hz)	1448	
								6.50-7.30(10H,m)		
8d	180-181.5	$C_{19}H_{16}N_2OS$	Calcd	71.22	5.03	8.74	10.01	2.10(3H,s,broadened)[a]	1635	310(16,700)
			Found	70.95	4.89	8.69	10.25	4.25(1H,d,J=7Hz)	1480	
								5.40(1H,d,J=7Hz)	1450	
								6.40(1H,m)		
								6.65-7.40(10H,m)		

a) Several drops of methanol-d_1 were added here to enhance solubility of compound.

Some trans-Dihydropyrimidones (9)

Compound	mp °C	Formula		Anal. Data C	H	N	S	Nmr Data ($CDCl_3$)δ	IR Data (KBr)cm^{-1}	UV Data λ_{max}^{EtOH} (ε)
9a	200	$C_{18}H_{14}N_2OS$	Calcd	70.56	4.61	9.14	10.47	4.10(1H,d,J=5.5Hz)[a]	1665	305(16,200)
			Found	70.71	4.65	9.06	10.34	5.50(1H,d,J=5.5Hz)	1490	
								6.80(2H,AB multiplet)	1455	
								7.10-7.50(10H,m)		
9b	185-187	$C_{19}H_{17}N_3OS$	Calcd	68.04	5.11	12.54	9.56	1.25(3H,t,J=7Hz)	1665	292(16,300)
			Found	67.87	5.03	12.47	9.77	2.75(2H,q,J=7Hz)	1480	
								4.10(1H,d,J=3Hz)	1455	
								5.60(1H,d,J=3Hz)		
								7.30(10H,s)		
9c	209-211	$C_{18}H_{16}N_2OS$	Calcd	70.10	5.23	9.08	10.40	3.05-3.85(5H,m)	1672	253(18,600)
			Found	69.93	5.14	9.12	10.43	4.65(1H,d,J=6Hz)	1522	
								6.90-7.40(10H,m)	1440	
9d	186-188	$C_{19}H_{16}N_2OS$	Calcd	71.22	5.03	8.74	10.01	2.00(3H,d,J=1Hz)	1650	309(14,100)
			Found	71.04	5.07	8.63	9.95	4.05(1H,s,broadened)	1480	
								5.40(1H,s,broadened)		
								6.15(1H,m)		
								7.00-7.40(10H,m)		

a) Several drops of methanol-d_1 were added here to enhance solubility of compound.

Some Diphenylacrylamides (11-15)

Compound	mp °C	Formula		Anal. Data C	H	N	S	Nmr Data ($CDCl_3$)δ	IR Data ($CHCl_3$) cm^{-1}
11	149-150	$C_{19}H_{16}N_2OS$	Calcd	71.22	5.03	8.74	10.01	2.25(3H,s,broadened)	3378
			Found	71.10	4.93	8.73	10.11	6.47(1H,m)	1666
								6.90-7.50(10H,m)	1611
								8.00(1H,s)	1528
								8.70(1H,broad,D_2O exchangeable)	1450
12	167-169	$C_{21}H_{20}N_2OS$	Calcd	72.38	5.79	8.04	9.20	1.10(3H,t,J=7Hz)	3375
			Found	72.28	5.72	7.96	9.31	2.30(3H,s)	1666
								2.50(2H,q,J=7Hz)	1528
								6.80-7.50(10H,m)	1450
								8.00(1H,s)	
								8.40(1H,broad,D_2O exchangeable)	
13	204-206	$C_{22}H_{16}N_2OS$	Calcd	74.13	4.53	7.86	9.00	6.80-7.80(14H,m)	3372
			Found	74.05	4.56	7.93	8.81	8.00(1H,s)	1672
								8.85(1H,broad,D_2O exchangeable)	1608
									1595
									1528
14	163-166	$C_{19}H_{16}N_2OS$	Calcd	71.22	5.03	8.74	10.01	2.15(3H,s,broadened)	3378
			Found	71.11	5.16	8.70	10.19	6.43(1H,m)	1667
								6.95(1H,s)	1611
								7.10-7.45(10H,m)	1595
								10.00(1H,broad,D_2O exchangeable)	1523
									1445
15	120-125	$C_{18}H_{14}N_2OS$	Calcd	70.56	4.61	9.14	10.47	6.90-7.60(12H,m)	3380
			Found	70.29	4.80	8.99	10.25	8.00(1H,s)	1678
								8.70(1H,broad,D_2O exchangeable)	1530
									1480

residue of 7e were subjected to column chromatography on silica gel (benzene eluent), 11 and 12 were eluted. The yields of 11-13 are included in Table I.

Isomerization of 8 to 9 with DABCO - A solution of 8 (0,10 g) in 10 ml of solvent (acetone for 8a-c, methanol for 8d) containing DABCO (0.2 g) was allowed to stand at room temperature for one month. After this time, the residue formed upon removal of the solvent was treated with 50 ml of water and extracted with 3-20 ml portions of methylene chloride. The organic layer was washed with 3-20 ml portions of water, dried over $MgSO_4$, and stripped of solvent to give 9 quantitatively.

Isomerization of 8a in Refluxing Chloroform - A solution of 8a (0.30 g, 0.98 mmol) in 35 ml of chloroform was heated under reflux during 16 days. After this time, addition of ether (50 ml) to the residue formed upon removal of the solvent left a white solid (0.25 g) which was recrystallized from methylene chloride-pentane to give 9a (0.22 g, 73%). The ether soluble fraction was concentrated to 10 ml whereupon addition of pentane (20 ml) caused precipitation of 15 (0.036 g, 12%).

Isomerization of 8d in Refluxing Chloroform - A solution of 8d (0.30 g, 0.94 mmol) in 35 ml of chloroform was heated under reflux during 16 days. After this time, addition of ether (50 ml) to the residue formed upon removal of the solvent left pure (by ir) 8d (0.15 g, 50%). Column chromatography (silica gel, benzene) of the ether soluble fraction afforded 14 (0.120 g, 80% based upon unrecovered 8d).

Reaction of 2-Aminothiazoline (7c) with Methyl Acrylate - A mixture of 2-aminothiazoline (1.02 g, 10 mmol) and methyl acrylate (0.9 ml, 0.86 g, 10 mmol) was heated on the steambath for 1.5 h, during which time solidification occurred. The yellow solid mass was recrystallized from chloroform-hexane to give 2,3,5,6-tetrahydro-7H-thiazolo|3,2-a|pyrimidin-7-one (1.0 g, 64%): mp 158-160°C; ir (KBr) 1660, 1545, 1472, 1461 cm^{-1}; nmr ($CDCl_3$) δ2.60 (2H triplet, J = 7 Hz), 3.10-4.05 (6H multiplet).

Anal. Calcd for $C_6H_8N_2OS$: C, 46.14; H, 5.16; N, 17.93. Found: C, 45.99; H, 5.21; N, 17.88.

Reaction of 1 with 2-Aminobenzimidazole (16a) - By the general procedure cited above, 1 (0.618 g, 3 mmol) and 16a (0.400 g, 3 mmol) furnished 17a (24 hr reaction, 0.385 g, 38%) as a THF insoluble solid: mp 238-240°C (lit.[2] mp 233-234°C); ir (KBr) 1700, 1635 cm^{-1}; nmr (CF_3CO_2H) δ5.20 and 6.05 (two 1H doublets, J = 7 Hz),

6.8-7.7 (m, 14 H).

The THF soluble fraction was subjected to column chromatography (silica gel, 30% ether-benzene) to afford 17b (0.305 g, 30%): mp 252-254°C; ir (KBr) 1695, 1635 cm^{-1}; nmr (CF_3CO_2H) δ4.70 and 5.90 (two 1 H doublets, J = 11 Hz), 6.40 (d, 1H, J= 8 Hz), 7.0 - 7.7 (m, 13 H).

Anal. calcd for $C_{22}H_{17}N_3O$: C, 77.86; H, 5.05; N, 12.38. Found: C, 78.14; H, 5.11; N, 12.26.

Reaction of 1 with 2-Amino-5-chlorobenzimidazole (16b) - By the general procedure, 1 (0.824 g, 4 mmol) and 16b (0.672 g, 4 mmol) produced, after 48 h , the THF insoluble 18a (0.180 g, 12%): mp 305-308°C; ir (KBr) 1695, 1635 cm^{-1}; nmr (CF_3CO_2H) δ5.10 and 6.00 (two 1 H doublets, J = 7 Hz), 6.75 - 7.8 (m, 13 H).

Anal. calcd for $C_{22}H_{16}N_3OCl$: C, 70.68; H, 4,31; N, 11.20. Found: C, 70.60; H, 4.26; N, 11.10.

The THF soluble fraction was treated with diethyl ether to yield insoluble 19 (0.750 g, 50%): mp 302-304°C; ir (KBr) 1700, 1640 cm^{-1}; nmr (CF_3CO_2H) δ4.65 and 5.80 (two 1 H doublets, J = 11 Hz), 6.20 (d, 1H, J = 8 Hz), 7.0 - 7.7 (m, 12 H).

Anal. calcd for $C_{22}H_{16}N_3OCl$: C, 70.68; H, 4.31; N, 11.20. Found: C, 70.76; H, 4.22; N, 11.32.

The ether soluble fraction was recrystallized from CH_2Cl_2-hexane to afford 18b (0.150 g, 10%): mp 309-311°C; ir (KBr) 1695, 1635 cm^{-1}; nmr (CF_3CO_2H) δ4.65 and 5.75 (two 1 H doublets, J = 11 Hz), 6.30 (br s, 1H), 6.95 - 7.7 (m, 12 H).

Anal. calcd for $C_{22}H_{16}N_3OCl$: C, 70.68; H, 4.31; N, 11.20. Found: C, 70.72; H, 4.40; N, 11.14.

Isomerization of 18a - A solution of 18a (0.170 g) in DMF (20 ml) was heated at 110°C during 48 h , then allowed to cool to room temperature, diluted with H_2O (100 ml), followed by extraction with ether (3 x 50 ml). The organic layer was washed with H_2O (3 x 50 ml), dried over $MgSO_4$, and stripped of solvent to give 18b quantitatively.

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9. All melting points were obtained on a Mettler FP 52 melting point apparatus and are uncorrected. Infrared spectra were taken on a Perkin-Elmer 337 spectrophotometer. Nmr spectra were recorded with a Varian T-60 spectrometer using tetramethylsilane as an internal standard. The elemental analyses were performed by Alfred Bernhardt Laboratories, West Germany.

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