AN UNUSUAL TERT-BUTYLAMINE MEDIATED CONVERSION OF 6-ARYL-7-FORMYL-2,4,5,8-TETRAHYDRO-1,3-DIOXA-5-AZOCINES TO 1,2,3,6-TETRAHYDROPYRIMIDINE DERIVATIVES

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An unexpected contraction of the 8-membered ring to a 6-membered one occurring when 6-aryl-7-formyl-2,4,5,8-tetrahydro-1,3-dioxa-5-azocines *II* were treated with tert-butylamine afforded 4-aryl-5-formyl-1-(1,1-dimethylethyl)-1,2,3,6-tetrahydropyrimidines *III*. Reaction conditions for the photorearrangement of chlorophenyl-substituted condensed isoxazolines *I* to *II* were worked out. The reaction sequence: 1,3-dipolar cycloaddition, photochemical rearrangement, treatment with tert-butylamine constitutes a new route to pyrimidine derivatives from 2*H*,4*H*,7*H*-1,3-dioxepine.

Isoxazolines are good precursors for the synthesis of β-hydroxyketones, β-hydroxynitriles, γ-aminoalcohols and α,β-unsaturated carbonyl-containing compounds[1]. As we have already shown[2-4], a 1,3-dipolar cycloaddition of nitrile oxides followed by a photoinduced rearrangement of isoxazolines opens a way for extension of an *n*-membered heterocycle to an *n* + 1 one, e.g. *I* → *II*. This paper is concerning the utilization of azocines *II* for syntheses.

The starting 6-aryl-7-formyl-2,4,5,8-tetrahydro-1,3-dioxa-5-azocines *II* were obtained by a photo-induced rearrangement of isoxazolines *I* (Table I). 8-Aryl-3,5,10-trioxa-9-azabicyclo[5.3.0]dec-8-enes *Ia*–*Ii* were prepared by a 1,3-dipolar cycloaddition of substituted benzenenitrile oxides to 2*H*,4*H*,7*H*-1,3-dioxepine[3]. Of the above-mentioned decenes *Ic*, *Ie*, *Ih*, and *Ii* are new compounds. Benzenenitrile oxides were synthesized in situ from the corresponding N-hydroxybenzenecarboximidoyl chlorides on treatment with triethylamine[5] with the exception of 2,4,6-trimethylbenzenenitrile oxide, which is stable[6]. The photorearrangement of compounds *IIe*, *IIf* and *IIh*, the unsuccessful preparation of which was reported in our previous paper[3], are new substances. In the formerly applied solvent (acetonitrile) an exchange of chlorine for hydrogen in the presence of triethylamine took place and the hydrogen chloride thus formed decomposed *II*. Further investigation showed ether to be an advantageous solvent for the photorearrangement of isoxazolines; this solvent offers also higher yields of *II* when compared with the previously used benzene, methanol

or acetonitrile. Addition of triethylamine to ether made it possible also to prepare 2-chloro, 3-chloro- and 2,4-dichloro-substituted derivatives *II*. The lower solubility of derivatives *I* in ether was compensated by addition of dimethoxyethane (5–25%). Preparation of *IIi* from 3,4-dichloro-substituted *Ii* failed due to its insolubility in the afore-mentioned combination of solvents; irradiation in methanol or acetonitrile led to formation of tars. Even upon a long-term irradiation 2,4,6-trimethylphenyl

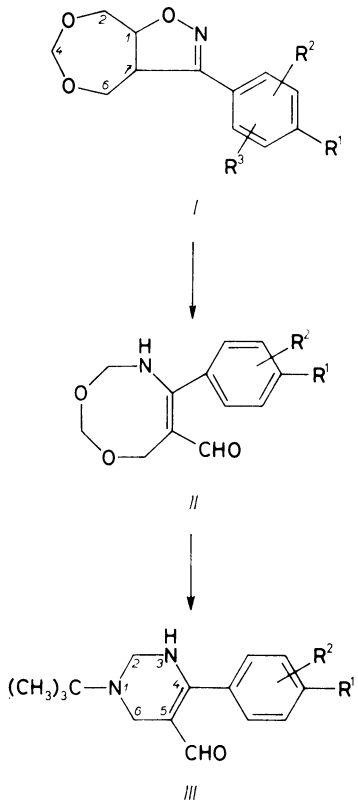
TABLE I
Characteristic data of *Ic*–*IIIg*

Compound	Formula (M.w.)	M.p., °C (Yield, %)	Calculated/Found			λ_{max}, nm (log ε)
			% C	% H	% N	
Ic	$C_{15}H_{19}NO_3$ (261·3)	109–100 (89)	68·94 69·12	7·33 7·45	5·36 5·61	243 (2·80)
Ie	$C_{12}H_{12}ClNO_3$ (253·7)	90–92 (78)	56·82 56·53	4·77 5·04	5·52 5·49	257 (3·21)
Ih	$C_{12}H_{11}Cl_2NO_2$ (288·1)	165–167 (80)	50·02 50·34	3·84 3·99	4·85 5·12	257 (3·25)
Ii	$C_{12}H_{11}Cl_2NO_3$ (288·1)	152–153 (75)	50·02 50·21	3·84 3·80	4·85 4·98	265 (3·27)
IIe	$C_{12}H_{12}ClNO_3$ (253·7)	158–160 (60)	56·82 57·12	4·77 5·04	5·52 5·49	296 (3·08)
IIf	$C_{12}H_{12}ClNO_3$ (253·7)	192–194 (71)	56·82 57·10	4·77 4·81	5·52 5·33	298 (3·12)
IIh	$C_{12}H_{11}Cl_2NO_3$ (288·1)	146–148 (41)	50·02 50·29	3·84 4·12	4·85 4·77	299 (3·10)
IIIa	$C_{15}H_{20}N_2O$ (244·3)	165–168 (55)	73·73 74·01	8·25 8·49	11·47 11·48	310 (3·14)
IIIb	$C_{16}H_{22}N_2O$ (258·4)	170–172 (42)	74·38 74·30	8·58 8·81	10·84 10·77	312 (3·08)
IIId	$C_{15}H_{19}FN_2O$ (262·3)	168–170 (45)	68·68 68·89	7·30 7·12	10·67 10·71	309 (3·12)
IIIe	$C_{15}H_{19}ClN_2O$ (278·8)	156–158 (51)	64·62 64·92	6·87 6·81	10·04 9·88	311 (3·07)
IIIf	$C_{15}H_{19}ClN_2O$ (278·8)	150–152 (40)	64·62 64·55	6·87 6·82	10·04 10·12	311 (3·09)
IIIg	$C_{15}H_{19}ClN_2O$ (278·8)	163–164 (48)	64·62 64·55	6·87 7·10	10·04 9·95	312 (3·14)

derivative *Ic* proved photostable. The structure of new derivatives *I* and *II* was ascribed on the basis of comparison of their spectral data with those of known compounds[2,3] (Tables II–V).

Investigation of the reactivity of azocines *II* revealed that at temperatures above 55°C, in acid medium or in the presence of oxidation or reduction agents, a decomposition to the hitherto unidentified product occured; compounds *II* did not enter cycloadditions to diazomethane, benzenenitrile oxide, acrylonitrile, or 2,3-dihydrofuran.

Azocines *II* react with methylamine to furnish seven products, but do not react with aromatic amines (Scheme 1); with tert-butylamine only one product was ob-



I

II

III

In formulae *I*–*III*: *a*, $R^1 = R^2 = H$ *b*, $R^1 = CH_3$; $R^2 = H$ *c*, $R^1 = CH_3$; $R^2 = 2\text{-}CH_3$; $R^3 = 6\text{-}CH_3$ *d*, $R^1 = F$; $R^2 = H$ *e*, $R^1 = H$; $R^2 = 2\text{-}Cl$ *f*, $R^1 = H$; $R^2 = 3\text{-}Cl$ *g*, $R^1 = Cl$; $R^2 = H$ *h*, $R^1 = Cl$; $R^2 = 2\text{-}Cl$ *i*, $R^1 = Cl$; $R^2 = 3\text{-}Cl$

SCHEME 1

tained in 40–55% yield. Its spectral data did not fit any of the expected addition or condensation products. Analysis of ^{1}H, ^{13}C NMR, IR, and UV spectral data indicated that heterocyclic enaminoaldehydes *III* (4-aryl-5-formyl-1-(1,1-dimethylethyl)-1,2,3,6,-tetrahydropyrimidines) were formed.

Intensive absorption bands in the IR spectrum at 1 650–1 640 cm^{-1} indicated the presence of an α,β-unsaturated carbonyl compound. The preserved enaminoaldehyde grouping in *III* was backed by the almost identical UV spectra with those of the starting compounds *II*. The aldehyde building block was evidenced by the

TABLE II

^{1}H NMR chemical shifts (δ, ppm) of 8-aryl-3,5,10-trioxa-9-azabicyclo[5,3,0]dec-8-enes *I*

Compound	H-1	H-2, H-4, H-6	H-7	H_{arom}
Ic[a]	4·99	3·74–4·84	3·60	6·88[b]
Ie	5·01	3·80–4·65	3·78	7·29–7·61
Ih	5·01	3·80–4·95	3·78	7·29–7·57
Ii	4·94	3·94–4·62	3·90	7·28–7·75

[a] 2·29 s (2 × CH_3), 2·27 s (CH_3); [b] singlet.

TABLE III

^{13}C NMR chemical shifts (δ, ppm) of *I*

Compound	C-1	C-2	C-4	C-6	C-7	C-8	C_{arom}
Ic[a]	81·49	70·14	98·93	66·69	55·52	157·90	138·82, 137·31, 128·88, 124·73
Ie	82·89	71·01	99·20	67·21	53·79	157·32	132·50, 131·98, 131·06, 129·98, 127·24
Ih	83·10	71·21	99·25	67·13	53·60	156·50	136·50, 133·22, 132·86, 129·87, 127·73, 127·00
Ii	84·05	69·10	98·56	66·36	51·73	155·61	134·29, 133·34, 131·01, 128·87, 128·69, 126·06

[a] 21·00 q (CH_3), 20·24 q (CH_3).

singlet at δ 8·90–9·00 in ^{1}H, and a doublet at δ 186·00–187·83 in the ^{13}C NMR spectra (Tables VI, VII). The singlet at δ 4·10–4·18 (H-2) was attributed to methylene protons between two nitrogen atoms. The chemical shift value was markedly lower than that of the starting 1,3-dioxa-5-azocines ($\delta \sim$ 5·00, O—CH_2—N) as a result of the influence of a lower electronegativity of nitrogen in the N—CH_2—N grouping. Also the δ values (3·54–3·69) were lower with respect to those for H-8 ($\delta \sim$ 4·80) of compound *II*, due to substitution of oxygen for nitrogen. The absence of a O—CH_2—O grouping, present in the starting *II*, was deduced from the NMR chemical shift data lacking the proper signals at δ 4·80 and 96·00, respectively. Difference in structure of the saturated moiety of compounds *III* and *II* was seen through considerable signal changes of the corresponding carbon atoms in the ^{13}C NMR

TABLE IV

^{1}H NMR chemical shifts (δ, ppm) of 6-aryl-7-formyl-2,4,5,8-tetrahydro-1,3-dioxa-5-azocines *II*

Compound	H-2[a]	H-4[a], H-8[a]	NH	CHO	H_{arom}
IIe	4·88	4·80	5·81	8·67	7·40–7·47
IIf[b]	5·02	4·79	5·54	8·91	7·43–7·56
IIh	4·89	4·82, 4·81	5·53	8·91	7·27–7·44

[a] Singlets; [b] CD_3SOCD_3.

TABLE V

^{13}C NMR chemical shifts (δ, ppm) of *II*

Compound	C-2	C-4	C-6	C-7	C-8	CHO	C_{arom}
IIe	96·57	74·81	112·82	162·43	66·64	190·71	136·46, 130·47, 130·10, 128·56
IIf[a]	94·87	74·02	111·06	161·10	64·16	188·34	138·44, 133·08, 130·19, 129·40, 129·84, 128·84
IIh	96·70	74·75	113·47	160·78	66·80	190·19	140·86, 136·89, 134·81, 131·43, 128·95, 128·71

[a] CD_3SOCD_3.

spectra. Chemical shifts for C-4 and C-8 of derivatives *II* were δ 74–75 and 64–66, respectively; for analogous C atoms in *III* the δ values were 57·86–58·65 (C-2) and 42·13–43·11 (C-6). These data are consistent with the suggested presence of adjacent nitrogen atoms. On the other hand, virtual identity of the corresponding part of the ^{13}C NMR spectra of *II* and *III* evidenced preservation of the NH—C=C—CHO

TABLE VI

^{1}H NMR chenical shifts (δ, ppm) of 4-aryl-5-formyl-1-(1,1-dimethylethyl)-1,2,3,6-tetrahydropyrimidines *III*

Compound	H-2	H-6	CH_3	NH	CHO	H_{arom}
IIIa	4·05	3·50	1·25	6·07	8·80	7·32
IIIb[a,b]	4·15	3·54	1·19	6·78	9·00	7·27–7·38
IIId	4·13	3·62	1·21	5·80	8·90	7·10–7·50
IIIe	4·10	3·62	1·21	5·47	8·97	7·41–7·43
IIIf	4·12	3·69	1·26	5·52	8·93	7·25–7·50
IIIg	4·18	3·54	1·16	5·89	8·91	7·44–7·49

[a] CD_3OD; [b] 2·39 s (CH_3).

TABLE VII

^{13}C NMR chemical shifts (δ, ppm) of *III*

Compound	C-2	C-4	C-5	C-6	C[a]	CH_3	CHO	C_{arom}
IIIa	57·86	110·23	162·66	42·13	54·24	26·21	187·57	133·34, 130·41, 129·52, 128·30
IIIb[b,c]	58·65	110·68	161·18	43·11	53·93	27·00	186·00	140·95, 132·32, 130·43, 130·35, 129·75
IIId	57·99	111·11	159·43	42·19	53·89	26·28	187·45	131·76, 131·41, 129·59, 116·02, 115·14
IIIe	58·09	110·81	160·67	42·23	53·81	26·45	187·83	133·61, 130·51, 129·68, 128·45
IIIg	58·04	111·25	159·32	42·19	53·66	26·68	187·28	136·62, 131·99, 130·88, 128·72

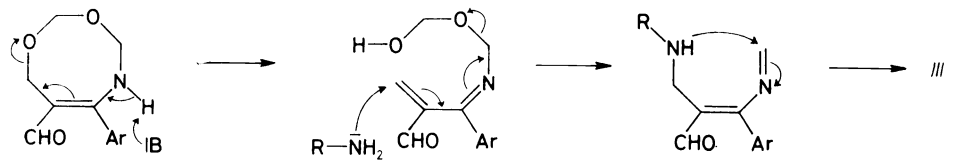
[a] Quaternary carbon; [b] CD_3OD; [c] 21·27 q (CH_3).

grouping. The ^1H and ^{13}C spectral data proved the presence of a tert-butyl group attached to the nitrogen atom.

The structure of *III* was further backed by mass spectra of *IIIa* and *IIIg* showing peaks of molecular radical ions (*m/z* 244 and 278, respectively). The most intensive peaks displayed the M − $(CH_3)_3C—N=CH_2$ species (*m/z* 159, 193).

1,3-Dioxazocines *II* gave with tert-butylamine 1,2,3,6-tetrahydropyrimidines *III* in best yields at room temperature in methanol. Nonetheless, the total conversion could not be achieved even at a longer reaction time. A greater excess of tert-butylamine can result in a greater yield of *III*. An excess of the amine is probably needed for trapping formaldehyde originating by fission of the fragment $HOCH_2OH$.

Reaction of *II* with tert-butylamine proceeded in less polar solvents as e.g. chloroform and dichloromethane very slowly, in line with the proposed polar mechanism (Scheme 2). The rearrangement might be due to the zwitterionic structure of *II*



SCHEME 2

considered on the basis of absorption bands in the IR spectra and the inability of *III* to give typical condensation reaction of aldehydes. An analogous zwitterionic compound was proposed to explain the process of some cycloaddition reactions of enaminocarbonyls[7]. A similar product — 4-phenyl-5-formyl-1-methyl-1,2,3,6-tetrahydropyrimidine — obtained as one of the seven products by reaction of *IIa* with methylamine could not be isolated in a pure form. Its structure could be proposed by comparing its NMR spectra with those of *III*. A complicated almost inseparable (HPLC) mixture was obtained on reacting *IIa* with benzylamine, hydrazine, phenylhydrazine or methylhydrazine. The presence of tetrahydropyrimidines in the mixture was unequivocally not evidenced.

EXPERIMENTAL

The melting points are uncorrected. The ^1H and ^{13}C NMR spectra of deuterochloroform solutions (unless otherwise stated) containing tetramethylsilane as an internal reference were measured with the respective Jeol JX-100 and Varian VXR-300 instruments. The UV spectra of methanolic solutions were measured in temperated cells with an M-40 (Zeiss, Jena) spectrophotometer, the values are given in $m^2\ mol^{-1}$. The reaction course and the purity of compounds were checked by thin-layer chromatography on silufol sheets (detection by UV_{254} light, or with iodine vapours). Toshiba GL-15 (15 W) quartz mercury lamp and a quartz reactor (300 ml) with a forced circula-

tion were employed for preparative photochemical reactions at 25°C. Substituted benzenehydroximic chlorides were obtained by chlorination[8] of the corresponding oximes, 2,4,6-trimethylbenzenenitrile oxide was prepared according to ref.[6]. Syntheses of compounds *Ia*, *Ib*, *Id*, *If*,*IIa*, *IIb*, *IId*, and *IIg* were already described[2,3].

8-Aryl-3,5,10-trioxa-9-azabicyclo[3.5.0]dec-8-enes *Ia*—*Ii*

Triethylamine (13 mmol) in ether (20 ml) was added to a solution of substituted N-hydroxybenzenecarboximidoyl chloride (10 mmol) and 2*H*,4*H*,7*H*-1,3-dioxepine (10 mmol) in ether (20 ml) at 0–5°C during 1 h. The mixture was stirred at an ambient temperature overnight, trimethylammonium chloride was filtered off, the solvent was distilled off under diminished pressure and the product was crystallized from chloroform–hexane.

8-(2,4,6-*Trimethylphenyl*-3,5,10-*trioxa*-9-*azabicyclo*[5.3.0]*dec*-8-*ene* (Ic) was prepared from 2,4,6-trimethylbenzenenitrile oxide (2·0 g, 12·3 mmol) and 2*H*,4*H*,7*H*-1,3-dioxepine (1·25 g, 12·3 mmol) in benzene (25 ml) by refluxing for 2 h, (checked by thin-layer chromatography), removing the solvent in vacuo and crystallization as in the preceding procedure.

6-Aryl-7-formyl-2,4,5,8-tetrahydro-1,3-dioxa-5-azocines *II*

A solution of the respective isoxazoline *I* (2·5 mmol) in ether (300 ml), or ether–dimethoxyethane if insoluble in the former was irradiated until the starting compound was consumed (checked by thin-layer chromatography, 2—5 h). The solution was concentrated under reduced pressure and the residue was triturated with hexane–ether (1 : 9). Triethylamine (2·5 ml) was added to derivatives substituted by chlorine.

4-Aryl-5-formyl-1-(1,1-dimethylethyl)-1,2,3,6-tetrahydropyridines *III*

Tert-butylamine (10 mmol) was added to a stirred solution of azocine *II* (2·5 mmol) in methanol (25 ml) at room temperature. After 2—4 days the reaction was over (checked by thin-layer chromatography); the solvent was removed under diminished pressure and the yellow oil was purified by chromatography on silica gel: chloroform eluted the unreacted starting material and the desired *III* was obtained by a gradient elution with methanol–chloroform (2—10%). The combined fractions were concentrated to 2 ml and ether was added to the residue (8 ml), accelerating thus crystallization. The final *III* was purified by crystallization from chloroform–hexane.

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