Synthesis and Photocyclization of some 4-(5)Arylethenylimidazoles

Gerd Lindgren, Karl-Erland Stensiö and Kerstin Wahlberg

National Defence Research Institute, Dept 4, S-901 82 Umeå, Sweden

Received July 16, 1979
Revised February 25, 1980

The synthesis of eleven 4-(5)arylethenylimidazoles and their separation into *cis* and *trans* isomers is described. Ir, uv, nmr, and mass spectrometric data of the compounds are given. The photocyclization of the unsubstituted and *p*-substituted compounds is reported.

J. Heterocyclic Chem., **17**, 679 (1980).

4-(5)Arylethenylimidazoles are of interest as inhibitors of the choline acetyltransferase system (acetyl-CoA: choline *O*-acetyltransferase, EC 2,3,1,6). Cavallito (1) and Baker (2) found that effective inhibitors consist of a π-donating and a π-accepting ring system joined by an ethylenic bond capable of giving coplanarity to the molecule. Inhibitors of this type are the arylethenylpyridines and arylethenylpyrimidines. Baker (3) showed that the type and positions of the substituents in the aryl ring are of importance for the inhibition of choline acetyltransferase.

Changing the nitrogen heterocycle to imidazole leads to another aromatic system which often shows pronounced biological activity. This paper describes the synthesis of eleven substituted 4-(5)arylethenylimidazoles and also some heteroaromatic systems derived from them by a photocyclization procedure. The biological activities of these compounds will be reported separately.

Most syntheses of 4-(5)substituted imidazoles are based on ring closure of α-amino (4) or α-hydroxy ketones (5), a rather cumbersome route often resulting in low yields and impure products. Only a few methods start with a preformed imidazole ring. For example, with the nitrosubstituted 4-(5)methylimidazoles it is possible to use the activated methylgroup in condensations with aldehydes (6) and in 4-(5)imidazolecarboxaldehyde the aldehydegroup has been used in malonic ester condensations (7).

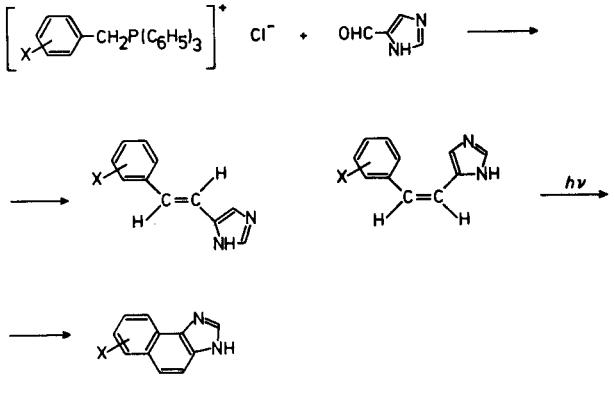
A convenient route (Scheme 1) to arylethenylimidazoles was found to be the Wittig reaction between 4-(5)imidazolecarboxaldehyde and phosphonium salts prepared from suitably substituted benzyl halides and triphenylphosphines.

4-(5)Imidazole carboxaldehyde was obtained by a convenient manganese dioxide oxidation of the corresponding alcohol in pyridine or acetonitrile. Stirring the heterogeneous system for about 20 minutes gave 75% yield of the aldehyde free of alcohol. 4-(5)Hydroxymethylimidazole is commerically available or may be synthesized from fructose (8).

The yields of arylethenylimidazoles were about 60% and a mixture of the *trans* and *cis* isomers were obtained by extraction. Earlier investigations have shown that choline acetyltransferase inhibition is dependent on the stereostructure of the inhibitor (9) and therefore both isomers were isolated from the reaction mixture. A clear

Scheme 1

4-(5)Arylethenylimidazoles Obtained by the Wittig Reaction (**1-11**), and Their Photocyclization Products (**12-15**)

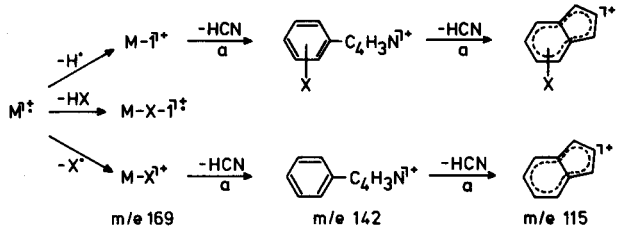


1 X = H	**6** X = 3-NO_2	**12** = cyclized **1**
2 4-CH_3	**7** 2-NO_2	**13** = cyclized **2**
3 3-CH_3	**8** 4-Cl	**14** = cyclized **8**
4 2-CH_3	**9** 3-Cl	**15** = cyclized **11**
5 4-NO_2	**10** 2-Cl	

11 the phenyl group is exchanged for an α naphthyl group

Scheme 2

Fragmentation Pattern of Compounds **1-11**: In Compound **11** the Phenyl Group is Exchanged for a Naphthyl Group



m/e 169 m/e 142 m/e 115

(a) Proved by metastable peaks.

0022-152X/80/040679-05$02.25

Table 1

Physical Data for 4-(5)Arylethenylimidazoles (Compounds **1-11**)

Compound No.	Isomer	M.p. (°C)	Uv λ max (ε) (a)	Ir (cm^{-1})	^{1}H-Nmr (b) Ar	vinyl	Imidazole	$ArCH_3$
1 (Phenyl)	*cis*	89-89.5	223 (14.3), 285 (8.8)	1395 (m)	7.3 (s, 5H)	6.50 (s, 2H)	6.70, 7.53	—
	trans	181.5	227 (12.2), 300 (27.1)	973 (s)	all signals 7.06-7.66			
2 (4-CH_3-phenyl)	*cis*	oil	226 (11.7), 286 (7.7)	1405 (w)	7.17 ($AA'BB'_q$, 4H)	6.41, 6.49 (AB_q, J = 12.5	6.74, 7.53	2.32 (s, 3H)
	trans	155.5-156	227 (12.8), 306 (29.9)	960 (s)		7.00-7.64 (m, 8H)		2.31 (s, 3H)
3 (3-CH_3-phenyl)	*cis*	83.5	225 (14.3), 285 (8.6)	1395 (m)	7.15 (m, 4H)	6.48 (s, 2H)	6.72, 7.54	2.31 (s, 3H)
	trans	134-138	226 (12.5), 301 (23.5)	965 (s)		7.03-7.65 (m, 8H)		2.34 (s, 3H)
4 (2-CH_3-phenyl)	*cis*	oil	224 (10.9), 263 (8.3)	1400 (w)	7.19 (s, 4H)	6.55 (s, 2H)	6.29 (d, J = 1) 7.49 (d, J = 1)	2.21 (s, 3H)
	trans	138.5-139	230 (10.8), 299 (22.5)	953 (s)		6.74-7.65 (m, 8H)		2.39 (s, 3H)
5 (4-NO_2-phenyl)	*cis*	140-142	254 (14.6), 355 (9.8)	1390 (w)	7.86 ($AA'BB'_q$, 4H)	6.57 (s, 2H)	6.84, 7.58	—
	trans	191-192	245 (8.9), 366 (17.1)	960 (s)	7.93 ($AA'BB'_q$, 4H)	7.16, 7.29 (AB_q, J = 16.5)	7.28, 7.72	—
6 (3-NO_2-phenyl)	*cis*	oil	215 (30.4), 273 (20.7)	1380 (w)	7.57-8.37 (m, 5H)	6.63 (s, 2H)	6.90 (c)	—
	trans	176-177	215 (13.5), 306 (19.5)	958 (s)	7.56-8.35 (m, 5H)	7.23 (s, 2H)	7.29 (c)	—
7 (2-NO_2-phenyl)	*cis*	102.5-103.5	239 (11.0)	1390 (w)	7.50-8.17 (m, 5H)	6.59, 6.74 (AB_q, J = 12.4)	6.35 (c)	—
	trans	153.5	214 (16.8), 278 (17.2), 295 (18.7)	962 (m)	all signals 6.93-7.98			—
8 (4-Cl-phenyl)	*cis*	84.5-85.5	228 (13.8), 291 (9.0)	1385 (w)	7.30 (s, 4H)	6.47 (s, 2H)	6.76 (d, J = 1) 7.56 (d, J = 1)	—
	trans	160	228 (10.7), 304 (28.8)	975 (s)	7.17-7.54 (m, 4H)	7.04 (s, 2H)	7.16, 7.66	—
9 (3-Cl-phenyl)	*cis*	oil	230 (15.0), 292 (8.9)	1390 (w)	7.25-7.38 (m, 4H)	6.49 (s, 2H)	6.73 (d, J = 1) 7.55 (d, J = 1)	—
	trans	136.5-137.5	233 (12.3), 303 (26.9)	950 (s)	7.15-7.50 (m, 5H)	7.05 (s, 2H)	7.68 (d, J = 1) (c)	
10 (2-Cl-phenyl)	*cis*	76-76.5	226 (10.6), 278 (6.6)	1390 (w)	7.14-7.54 (m, 5H)	6.55 (s, 2H)	6.52 (c)	
	trans	112-114	232 (11.0), 301 (26.3)	950 (s)	all signals 6.90-7.78			
11 (α-naphthyl)	*cis*	92-97	220 (54.7), 292 (6.7)	1403 (w)	7.27-8.08 (m, 8H)	6.77, 6.89 (AB_q, J = 12)	6.14 (d, J = 1) (c)	
	trans	200-201	229 (32.9), 322 (20.0)	958 (s)	all signals 6.92-8.38			

(a) λ max nm, ε × 10^{-3} $mole^{-1}$ cm^{-1}. (b) When not otherwise stated, a figure has the character of a (s, 1H) signal. All spectra were measured in methanol-d_4 except the *trans* isomer of compound **11**, which was measured in methanol-d_4-deuteriochloroform (1:1). (c) One proton obscured by aromatic protons.

Table 2

Characteristic Mass Fragments of Compounds **1-11** Given in % Relative Abundance

Compound Number	Isomer	M	M-1	M-X	M-X-1	M-28	M-X-27	M-55	M-X-54	m/e 119	m/e 92	m/e 91
1 (Phenyl)	*cis*	100	100			40		60				
	trans	75	100			40		45				
2 (4-CH_3-phenyl)	*cis*	100	90	50	15	50	10	20	30			20
	trans	100	100	35	10	50	10	20	20			20
3 (3-CH_3-phenyl)	*cis*	100	75	60	15	40	10	20	30			20
	trans	95	100	35	10	45	10	20	20			20
4 (2-CH_3-phenyl)	*cis*	75	30	100	20	35	35	30	75			20
	trans	100	65	100	20	60	60	30	50			45
5 (4-NO_2-phenyl)	*cis*	100	95	25	60		35		65			
	trans	95	100	20	55		30		50			
6 (3-NO_2-phenyl)	*cis*	100	75	15	80		30		80			
	trans	100	95	20	90		40		80			
7 (2-NO_2-phenyl)	*cis*	40	5	40	20		30		50	70	100	50
	trans	50	10	40	20		20		50	70	100	45
8 (4-Cl-phenyl)	*cis*	100	80	60	35	30	20	20	75			
	trans	100	100	40	30	40	15	25	60			
9 (3-Cl-phenyl)	*cis*	100	90	25	30	50	15	20	55			
	trans	95	100	35	30	35	15	20	50			
10 (2-Cl-phenyl)	*cis*	20	5	100	15	5	35	10	50			
	trans	30	5	100	10	5	45	10	35			
11 (α-naphthyl)	*cis*	100	95			25		40				
	trans	95	100			30		40				

Table 3

High Resolution Ms Data of Compound **7** and the Corresponding Pyrrole Derivative

2-Nitrophenylethenylimidazole				2-Nitrophenylethenylpyrrole			
Fragment, m/e	Relative Intensity, %	Elemental Composition	Error, mu	Fragment, m/e	Relative Intensity, %	Elemental Composition	Error
215	45	$C_{11}H_9N_3O_2$	−1.5	214	100	$C_{12}H_{10}N_2O_2$	−3.7
119	90	C_7H_5NO	0.2	119	25	C_7H_5NO	0.0
95	40	$C_4H_3N_2O$	1.1	94	65	C_6H_4NO	−2.3
92	100	C_6H_4O	0.5	92	85	C_6H_4O	3.0
91	60	C_6H_5N	3.0	91	45	C_6H_5N	1.8
81	95	$C_4H_5N_2$	−0.3	80	80	C_5H_6N	0.1

Table 4

Elemental Analyses of 4-(5)Arylethenylimidazoles (Compounds **1-11**) and Some Photocyclized Compounds Thereof

Compound No.	Arylgroup	Empirical Formula	Calcd., % C	H	N	Isomer	Found, % C	H	N
1	Phenyl	$C_{11}H_{10}N_2$	77.62	5.92	16.46	*trans*	77.51	5.90	16.34
						cis	77.43	5.73	16.31
2	4-CH_3-Phenyl	$C_{12}H_{12}N_2$	78.23	6.57	15.20	*trans*	78.01	6.42	15.13
						cis	78.57	6.27	14.91
3	3-CH_3-phenyl	$C_{12}H_{12}N_2$	78.23	6.57	15.20	*trans*	78.21	6.85	15.12
						cis	78.28	6.92	15.13
4	2-CH_3-phenyl	$C_{12}H_{12}N_2$	78.23	6.57	15.20	*trans*	78.34	6.67	15.07
						cis	78.42	6.39	15.43
5	4-NO_2-phenyl	$C_{11}H_9N_3O$	66.32	4.55	21.09	*trans*	66.21	4.77	21.04
						cis	66.14	4.63	20.95
6	3-NO_2-phenyl	$C_{11}H_9N_3O$	66.32	4.55	21.09	*trans*	66.47	4.47	21.03
						cis	66.01	4.92	21.09
7	2-NO_2-phenyl	$C_{11}H_9N_3O$	66.32	4.55	21.09	*trans*	66.57	4.72	21.05
						cis	66.49	4.28	21.33
8	4-Cl-phenyl	$C_{11}H_9ClN_2$	64.56	4.43	13.69	*trans*	64.31	4.38	13.93
						cis	64.64	4.31	13.85
9	3-Cl-phenyl	$C_{11}H_9ClN_2$	64.56	4.43	13.69	*trans*	64.62	4.26	13.62
						cis	64.29	4.75	13.41
10	2-Cl-phenyl	$C_{11}H_9ClN_2$	64.56	4.43	13.69	*trans*	64.87	4.47	13.47
						cis	64.73	4.21	13.56
11	α-naphthyl	$C_{15}H_{12}N_2$	81.79	5.49	12.71	*trans*	81.43	5.71	12.78
						cis	81.56	5.63	12.88
12	cyclized compound **1**	$C_{11}H_8N_2$	78.55	4.79	16.66	—	78.80	4.83	16.56
13	cyclized compound **2**	$C_{12}H_{10}N_2$	79.10	5.53	15.37	—	79.25	5.62	15.30
14	cyclized compound **8**	$C_{11}H_7ClN_2$	65.20	3.48	13.82	—	65.11	3.49	13.85
15	cyclized compound **11**	$C_{15}H_{10}N_2$	82.55	4.61	12.83	—	82.61	4.68	12.69

analytical separation of *cis* and *trans* isomers was achieved by hplc. Separation by tlc was not possible.

A good and fast separation of the two isomers was possible on a Sephadex G 15 column. Since K_{av} values (10) are much higher than 1, the separation is not governed by a gel filtration mechanism. It is known that Sephadex gels reversibly adsorb molecules with π-electron systems (11). Since the planarity of the arylethenylimidazoles influences the overall π-density and facility for charge transfer interactions it is not surprising that good separation is obtained for the *cis* and *trans* isomers.

The eluent for these separations was a solution of hydrochloric acid and sodium chloride. An acid medium was necessary to get the substances in solution and the separated isomers were isolated by extraction with chloroform after making the eluate alkaline. By increasing the ionic strength the retention was decreased. For all isomers except the naphthyl compounds 0.1*M* hydrochloric acid/0.05*M* sodium chloride was found to be adequate for a good separation.

The *cis* isomers always eluted first with K_{av} values around 5.5-7.5 and the planar *trans* isomers more prone to charge transfer interactions, eluted considerably later (K_{av} 11-19).

The π-electron-rich *cis* isomer of **11** had K_{av} 20 and the *trans* isomer only eluted with a considerably increased

ionic-strength. There are only small differences between positional isomers but a significant difference in the series of compounds with different aryl groups and the substances elute in the following order: phenyl (smallest retention volume), nitrophenyl, methylphenyl, chlorophenyl and naphthyl. The same order holds for both *cis* and *trans* isomers and a more lipophilic compound has a larger retention volume. The retention volume is roughly linearly dependent on the group partition parameter described by Craig (12).

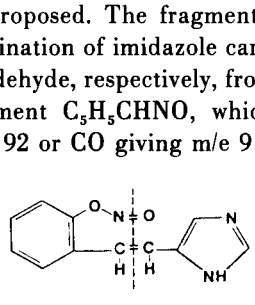
The ir spectra of the *trans* isomers show strong C-H out-of-plane-bending absorption of the vinyl group in the region 950-975 cm^{-1} (13). This absorption is absent for the *cis* isomers, all of which have a characteristic weak band at 1380-1405 cm^{-1} attributed to in-plane C-H bending (14). (Table 1). The uv spectra of substituted 4-(5)arylethenylimidazoles show two main absorption bands (Table 1) and the shifts in wavelength and intensity observed when going from the *trans* to the *cis* isomers are as expected (15).

^{1}H-nmr data (Table 1) show that in general the *trans* compound gives a more complicated spectrum than the corresponding *cis* compound. For example, in compounds **5,6,8** and **9** the *trans* vinyl protons are deshielded about 0.5 ppm compared to the *cis* vinyl protons. This indicates that the *trans* isomers have a planar structure and the *cis* isomers have not (16).

A generalized description of the mass fragmentation of compounds **1-11** is formulated in Scheme 2. The mass fragment and their relative intensities are given in Table 2. Most compounds have a base peak at M or M-1 mass units. However in the *o*-methyl (**4**) and *o*-chloro (**10**) compounds the base peak is formed by elimination of the substituent from the phenyl ring.

The mass spectra of *cis* and *trans* **7** show, as well as the same fragmentation pattern as the mass spectra of **5** and **6** prominent peaks at m/e 119 (base peak), 95, 92, 91 and 81. The corresponding fragments were also obtained from 2-nitrophenylethenylpyrrole (Table 3).

Based on exact mass determination (high resolution mass spectrometry) and metastable ions, the following interpretation is proposed. The fragment m/e 119 corresponds to an elimination of imidazole carboxaldehyde and pyrrole carboxaldehyde, respectively, from the parent ion, giving the fragment C_5H_5CHNO, which can eliminate HCN giving m/e 92 or CO giving m/e 91.



The fragment m/e 95 (m/e 94) corresponds to imidazole-C≡O (pyrrole-C≡O). This interpretation is in agreement with that reported for 2-nitrophenylethenylbenzene (17).

The fragment m/e 81 (m/e 80) is a common feature in mass spectra of alkylimidazoles (alkylpyrroles) and is formed when the molecule is degraded to pyrimidinium ion (pyridinium ion). This ion is a predominant peak in the mass spectrum of **7** (2-nitrophenylethenylpyrrole). This fragment is however not observed in the mass spectra of any of the other arylethenylimidazoles.

Earlier investigations have shown that *trans* stilbenes and stilbazoles rearrange photochemically to the *cis* isomers, which then undergo ring closure to a tricyclic hydrocarbon or a heterocycle. Oxidation, *e.g.*, with atomspheric oxygen gives an aromatic structure (18). In the present case it was found that photocyclization is an excellent route to planar systems (Scheme 1) which were of interest to test for choline acetylase inhibition.

To avoid mixtures of isomers the photocyclization was first tested on the unsubstituted compounds (**1,11**) and the *p*-substituted ones (**2,5,8**). The *p*-nitro compound failed to cyclize, the starting material being recovered.

EXPERIMENTAL

All melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 225 grating infrared spectrophotometer. Ultraviolet spectra were measured in absolute ethanol with a Beckman 25 spectrophotometer. Mass spectra were recorded with an LKB 9000 instrument. The high resolution mass spectra were performed at Varian Application Laboratory in Bremen, West Germany. The nmr spectra were measured with a 60 MHz Varian NV 14 spectrometer and chemical shifts are given as δ ppm relative to tetramethylsilane as internal standard. The thin layer chromatographic system used a silica gel (60, F-254, Merck) with ethyl accetate-propanol-ammonia, (45:35:20, v:v:v) as eluant unless otherwise is specified. Echtblausalz B (1% water solution) or Dragendorff's reagent were used to detect the compounds. Elemental analysis were performed by the analytical laboratory of the National Defence Research Institute on a Hewlett Packard 802 instrument (Table 4).

4-(5)Hydroxymethylimidazole.

4-(5)Hydroxymethylimidazole hydrochloride (8) was dissolved in water, made alkaline with saturated sodium carbonate and evaporated *in vacuo*. The residue was extracted with 99.5% ethanol, the extract was filtered, decolorized with activated carbon and the solvent was evaporated. The oily free base (yield 86%) crystallized in some hours.

4-(5)Imidazolecarboxaldehyde

The free base of 4-(5)hydroxymethylimidazole (0.1 mole, 9.8 g.) dissolved in pyridine (500 ml.) was heated to 100° with stirring. Manganese dioxide (100 g., Merck, precipitated, active) was added and after 20 minutes the reaction mixture was cooled, filtered (Celite), and evaporated *in vacuo*. The residue was dissolved in methanol, from which the product crystallized, 7.6 g. (79%), m.p. 170.5-171°, lit. (19) m.p. 173-174°. Silica gel tlc with 1-butanol-acetic acid-water (4:1:1) as eluent was used to follow the reaction, R_f (alcohol) 0.35, R_f (aldehyde) 0.50.

Aryltriphenylphosphonium Chlorides.

A mixture of one equivalent of the appropriate benzyl (or naphthylmethyl) chloride and one equivalent of triphenylphosphine (Merck) was stirred vigorously. The temperature was raised slowly and a clear solution was obtained, which started to solidify at about 80-120°. The crude product was cooled, washed repeatedly with ethyl ether to remove excess of triphenylphosphine and the white crystals were collected, yield 70-95%.

4-(5)Arylethenylimidazoles.

A solution of sodium (0.015 mole) in 20 ml. of absolute ethanol was

added dropwise during 2 hours to a stirred refluxing solution of aryltriphenylphosphonium chloride (0.015 mole) and 4-(5)imidazolecarboxaldehyde (0.015 mole) in 35 ml. of absolute ethanol. After about 3 hours, the solution was cooled, filtered and evaporated. The residue was suspended in water, acidified with hydrogen chloride and washed with ethyl ether to remove triphenylphosphonium oxide. The aqueous layer was made alkaline with sodium hydroxide and extracted with ethyl ether. The organic layer was dried and evaporated to give 50-90% of a crude mixture of *trans*- and *cis*-4-(5)arylethenylimidazole.

2-(2-Nitrophenylethenyl)pyrrole.

The synthesis was performed as for the 4-(5)arylethenylimidazoles. The residue was suspended in water, acidified with hydrochloric acid and extracted with ethyl ether. The ether extract was treated with sodium hydroxide, dried and evaporated. From the residue the title compound was isolated by preparative tlc (silica gel PF_{254} with chloroform as eluent).

Chromatographic Separation of *trans*- and *cis*-4-(5)Arylethenylimidazoles.

Analytical gel filtration was performed on a column of 0.9 cm × 28 cm Sephadex G 15 (G 25 for α-naphthylethenylimidazole) with an eluent consisting of 0.05*M* sodium chloride plus 0.01*M* hydrochloric acid. The flow rate was maintained at 1.5 ml. $minute^{-1}$ with a peristaltic pump. About 1 mg. of sample was separated and the eluted components were detected by uv (ISCO Type Ua5 optical unit). For preparative separation of about 1 g. samples, a 3.7 cm × 70 cm column was used with the same gel and eluent as described above. The separated *cis* and *trans* components were isolated by extraction with ethyl ether of the alklaine eluate. The *cis* and *trans* isomers could also be separated by hplc on a 10 μ silica gel column (30 cm × 3.9 mm i.d.) with 2 ml. $minute^{-1}$ of chloroform-methanol (96:4) as eluent.

Photocyclisation of 4-(5)Arylethenylimidazoles.

The photochemical reactions were carried out using a Hanau 150 W high-pressure mercury lamp (TQ150) surrounded by a water-cooled quartz jacket. The jacketed lamp was placed in the solution which was stirred with a magnetic stirrer. The crude mixture of *cis*- and *trans*-4-(5)arylethenylimidazole (0.002 mole) and iodine (0.10 g.) was dissolved in 400 ml. of absolute ethanol. The solution was irradiated for 24 hours, treated with solid sodium thiosulphate to destroy excess of iodine, filtered and evaporated. The residue was suspended in water, acidified with hydrogen chloride, washed with ethyl ether, made alkaline with sodium hydroxide and extracted with chloroform. The extract was dried, evaporated and the residue recrystallized from absolute ethanol-acetone mixture, yield ≈ 50%. On tlc the cyclized compounds gave, in contrast to the uncyclized compounds, no colour with Echtblausalz. Elution was effected with chloroform-methanol (9:1) on silica gel plates and the cyclized products always had higher R_f value than the starting material.

Physical data of the cyclized compounds are given as follows.

Compound **12**.

This compound had m.p. 177.5-178.5°; uv: λ max nm (ε × 10^{-3}) 219 (44.6), 238 (49.0), 245 (47.2); ms: m/e (relative intensity) 168 (100, M), 141 (10, M-27), 140 (30, M-28), 114 (15, M-54), 113 (10, M-55).

Compound **13**.

This compound had m.p. 257-258°; uv: λ max nm (ε × 10^{-3}) 226 (38.9), 240 (44.6), 245 (41.7); ms: m/e (relative intensity) 182 (100, M), 181 (90), 154 (20, M-28), 127 (20, M-55).

Compound **14**.

This compound had m.p. >300; uv: λ max nm (ε × 10^{-3}) 219 (31.7), 243 (56.2), 248 (54.0); ms: m/e (relative intensity) 204 (33, M + 2), 202 (100 M), 174 (10, M-28), 167 (10, M-35), 140 (25, M-35-27), 113 (10, M-35-34).

Compound **15**.

This compound had m.p. 216.5-217°; uv: λ max nm (ε × 10^{-3}) 258 (70.0), 306 (14.7); ms: m/e (relative intensity) 218 (100, M), 190 (25, M-28), 163 (10, M-55).

Acknowledgement.

The authors are very grateful to Johan Santesson for his interest and helpful discussions during this work, and to Lars Åkerström for technical assistance.

REFERENCES AND NOTES

(1) R. C. Allen, G. L. Carlson and C. J. Cavallito, *J. Med. Chem.*, **13**, 909 (1970).

(2) R. E. Gibson and B. R. Baker, *ibid.*, **17**, 1290 (1974).

(3) B. R. Baker and R. E. Gibson, *ibid.*, **15**, 639 (1972).

(4) H. Bredereck, R. Gompper, H. G. v. Schuh and G. Theilig, *Angew. Chem.*, **71**, 753 (1959).

(5) H. Weidenhagen, *Ber.*, **68**, 1953 (1935).

(6) W. J. Ross, W. B. Jamieson and M. C. McCowen, *J. Med. Chem.*, **15**, 1035 (1972).

(7) R. G. Jones and K. G. McLanghlin, *J. Am. Chem. Soc.*, **71**, 2444 (1949).

(8) J. R. Totter and W. J. Darby, *Org. Synth., Coll. Vol. III*, 460.

(9) H. L. White and C. J. Cavallito, *Biochim. Biophys. Acta*, **206**, 24 (1970).

(10) $K_{av} = (V_e - V_o)/(V_t - V_o)$ according to T. L. Laurent and J. Killander, *J. Chromatog.*, **14**, 317 (1964).

(11) J. Porath, *Biochim. Biophys. Acta*, **39**, 193 (1960).

(12) P. N. Craig, *J. Med. Chem.*, **14**, 680 (1971).

(13) A. R. Katritzky, A. J. Boulton and D. J. Short, *J. Chem. Soc., Perkin Trans. 1*, 1519 (1960).

(14) N. Sheppard and D. M. Simpson, *Quart. Rev. Chem. Soc.*, **6**, 1 (1952).

(15) F. H. Clarke, G. A. Felock, G. B. Silverman and C. M. Watrick, *J. Org. Chem.*, **27**, 533 (1962).

(16) H. A. P. de Jongh and H. Wynberg, *Tetrahedron*, **21**, 515 (1965).

(17) H. Güsten, L. Klasinc, V. Kramer and J. Marsel, *Org. Mass. Spectr.*, **8**, 323 (1974).

(18) E. V. Blackburn and C. J. Timmons, *Quart. Rev.*, **23**, 482 (1969).

(19) K. Hofman "The Chemistry of Heterocyclic Compounds", Vol. I, Interscience, New York, N.Y., 1953, p. 55.