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Cycloaddition Reactions of some Analogs of the Acridizinium Ion (1)

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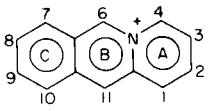
The 1-aryl-2-imidazo[1,2-*b*]isoquinolin-4-ium system (**3** and **4**), prepared by the action of aniline, or a suitable aniline derivative upon 2-phenacyl-3-chloroisoquinolinium bromide undergoes cycloaddition reactions only with the more nucleophilic alkenes such as cyclopentadiene or 9-vinylcarbazole.

The pyrazino[1,2-*b*]isoquinolin-5-ium-2-oxide (**8-10**) system reacts with nucleophilic alkenes more readily than does the acridizinium system 1. For both systems the cycloaddition appears to occur across the *meso* position of the central ring.

Although the recent work of Fields and Miller (2) has made it clear that the characteristic ability (3) of acridizinium salts (**1**) to undergo cycloaddition reactions survives



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drastic change in the nature of ring C, very little is known about the effect of modification of ring A. This report concerns two such modified systems, the 1*H*-imidazo[1,2-*b*]isoquinolin-4-ium (Chart I) and the pyrazino[1,2-*b*]isoquinolin-5-ium systems (Chart II).

The synthesis of the imidazoisoquinolinium derivatives (**3** and **4**) was accomplished by a modification of the method developed earlier (4) for the preparation of 1-arylimidazo[1,2-*a*]pyridinium salts.

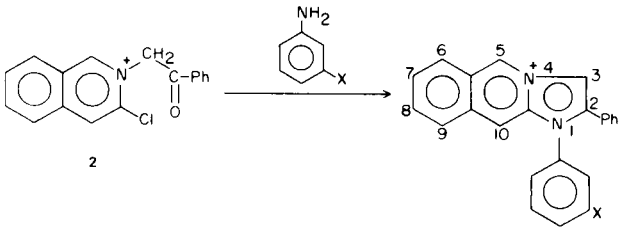
2-Phenacyl-3-chloroisoquinolinium (**2**) is understandably less reactive than 2-bromo-1-phenacylpyridinium bromide yet does give a 73% yield of the imidazolo derivative **3** when refluxed in acetonitrile with aniline. The less basic trifluoromethylaniline gave only a 38% yield of **4**.

The study of a series of 9-substituted acridizinium salts has shown (5) that the rate of cycloaddition of styrene is dependent upon the electron-withdrawing capacity of the 9-substituent, a phenomenon explicable by the assumption that the rate is controlled by the degree of electron-deficiency at the 6 (*para*) position. It is not surprising that the new heterocyclic system has proved less prone to undergo cycloaddition than the acridizinium system, since the presence of a second nitrogen atom at position 1 of the imidazoisoquinolinium system (**3**), and the consequently greater delocalization of the positive charge, results in the *meso* position adjacent to the bridgehead nitrogen being less electron-deficient. For example, neither styrene (6,7) nor *N*-(1-cyclohexenyl)morpholine (6) which react readily with the acridizinium ion would react with the 1-phenylimidazo derivative **3**. Successful cycloadditions were carried out using the very reactive cyclopentadiene with **3** to yield **5** and *N*-vinylcarbazole with **4** to yield **6**. Both products are probably mixtures of stereoisomers.

It was shown earlier (9) that when 3-oximidomethylisoquinoline was quaternized with bromoacetone (presumably yielding **7**, Z = O, R = CH_3) it cyclized readily to afford the oxide (**9**) of 3-methyl-2-azaacridizinium. Through use of chloroacetaldoxime (**10**) and phenacyl bromide in place of bromoacetone we have now made the oxides (**8-10**) of 2-azaacridizinium and its 3-phenyl derivative.

Since the modification of the acridizinium system by the replacement of the carbon at position 2 by an amine oxide group should be expected to enhance rather than dissipate the positive charge at the 6 (*meso*) position, it would be expected that the new aza oxide salts (**8-10**)

CHART I



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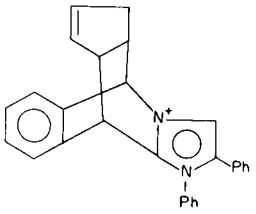
3, X = H
4, X = CF_3



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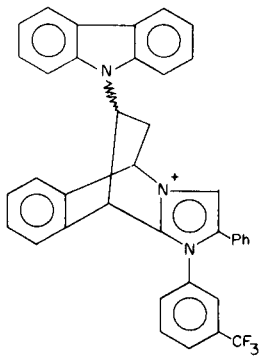

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CHART II

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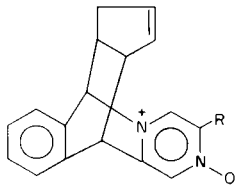
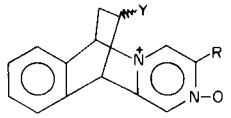
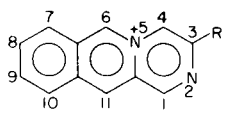
8, R = H
9, R = Me
10, R = Ph



11, R = H
12, R = Me
13, R = Ph



14, R = H
15, R = Me
16, R = Ph



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would undergo cycloaddition reactions as easily as does the acridizinium ion. This has been found to be the case, for each of the three aza oxide perchlorates (**8-10**) was found to react rapidly at room temperature with cyclopentadiene, *N*-vinyl-2-pyrrolidinone, 9-vinylcarbazole and ethyl vinyl ether. The results have been summarized in Table I. It is presumed that all cycloaddition products are mixtures of stereoisomers, although only one such product, that from the reaction of 9-vinylcarbazole with the oxide (**9**) of 3-methyl-2-azaacridizinium perchlorate, was actually separated during crystallization.

One objective of this project was to prepare 2-azaacridizinium salts (**17**) and compare the cycloaddition of these with that of the oxides (**8-10**) and the related acridizinium derivatives. Although we did not succeed in preparing the parent compound (**17**, R = H), it was found that the 3-phenyl derivative (**17**, R = Ph) could be prepared by the action of phosphorus tribromide on the oxide **10**. It was found that the aza compound (**17**, R = Ph) undergoes cycloaddition with 1-vinyl-2-pyrrolidinone. In order to establish a basis for comparison of the rate of addition of the new 2-azaacridizinium systems with acridizinium, and with each other, pseudo first order rate constants were determined for the reaction with styrene. The results are to be found in Table II.

It would appear that replacement of the carbon at position 2 of acridizinium by an amine oxide group results in a significant enhancement of rate of cycloaddition. Understandably the amine **17** is significantly slower than its oxide **10**.

EXPERIMENTAL

Melting points were taken in capillaries using the Thomas-Hoover apparatus and are uncorrected. Elemental analyses were by Janssen Pharmaceutica Research Laboratories, Beerse, Belgium and by MHW Laboratories, Garden City, Michigan.

3-Chloro-2-phenacylisoquinolinium Bromide (**2**).

Five g. (30.5 mmoles) of 3-chloroisoquinoline (11) and 12 g. (60 mmoles) of phenacyl bromide was heated together at 110-115° for 0.5 hour. The cooled melt was triturated with acetone and the crude product recrystallized from methanol-ethyl acetate affording 7.0 g. (65%) of product, m.p. 171°.

Anal. Calcd. for $C_{17}H_{13}BrClNO$: C, 56.29; H, 3.61; N, 3.86. Found: C, 56.25; H, 3.50; N, 3.64.

1,2-Diphenyl-1*H*-imidazo[1,2-*b*]isoquinolin-4-ium Perchlorate (**3**).

A solution of 4.5 g. (12.4 mmoles) of 3-chloro-2-phenacylisoquinolinium bromide (**2**) and 4.5 g. (48.3 mmoles) of freshly distilled aniline in 50 ml. of anhydrous acetonitrile was refluxed for 18 hours, and then poured into 200 ml. of ethyl acetate. The product which was obtained on cooling was crystallized from boiling water to which 5 g. of sodium bromide was added. Recrystallization of the resulting product from methanol-ethyl acetate afforded 3.5 g. (73%) of yellow fluorescent crystals; uv max (abs. ethanol) 250 mμ (log ε 4.46), 273 (4.40), 375 (3.85)

TABLE I

Cycloaddition of Amine Oxides of 2-Azaacridizinium Perchlorates (**8-10**) in Acetonitrile at Room Temperature

Alkenophile R	Alkenophile No.	Alkene	Product No.	Product Y	Time Hr.	Yield %	M.p., °C (a)	Formula	Analyses, % (b) C	H	N
H	**8**	Cyclopentadiene	**11**		1	83	239.5	$C_{17}H_{15}ClN_2O_5$	56.28 56.72	4.17 4.62	7.72 7.42
H	**8**	*N*-vinyl-2-pyrrolidinone	**14**	2-pyrrolidinone-1-yl	2	86	220	$C_{18}H_{18}ClN_3O_6$	53.01 53.20	4.44 4.43	10.30 9.87
H	**8**	9-Vinyl-carbazole	**14**	9-Carbazyl	2	80	222-223	$C_{26}H_{20}ClN_3O_5 \cdot 0.5H_2O$	62.59 62.38	4.24 4.19	8.42 8.18
H	**8**	Ethyl vinyl ether	**16**	OEt	2	68	162-164	$C_{16}H_{17}ClN_2O_6$	52.11 51.86	4.65 4.64	7.60 7.64
Me	**9**	Cyclopentadiene	**12**		1	55	253-254	$C_{18}H_{17}ClN_2O_5$	57.37 57.61	4.55 4.69	7.44 7.35
Me	**9**	*N*-Vinyl-2-pyrrolidone	**15**	2-pyrrolidinone-1-yl	6	86	212-213	$C_{19}H_{20}ClN_3O_6 \cdot 0.5CH_3CN$	54.30 54.10	4.90 4.76	11.08 10.97
Me	**9**	9-Vinyl carbazole	**15**	9-Carbazyl	3	72 (c)	215-216 (d) 202-203 (e)	$C_{27}H_{22}ClN_3O_5$	64.35 64.73 64.35 64.24	4.40 4.17 4.40 4.39	8.34 8.17 8.34 8.26
Me	**9** (f)	Ethyl vinyl ether	**15**	OEt	1	85	216-216.5	$C_{17}H_{19}BrN_2O_2$	56.20 56.17	5.27 5.64	7.71 7.55
Ph	**10**	Cyclopentadiene	**13**		1	85	245.5	$C_{23}H_{19}ClN_2O_5$	62.94 62.91	4.36 4.03	6.38 6.26
Ph	**10**	*N*-Vinyl-2-pyrrolidone	**16**	2-pyrrolidone-1-yl	0.1	90	217	$C_{24}H_{22}ClN_3O_6$	59.57 59.69	4.58 4.79	8.68 8.25
Ph	**10**	9-Vinyl carbazole	**16**	9-Carbazyl	0.1	76	238.5	$C_{32}H_{24}ClN_3O_5$	67.90 68.26	4.27 4.25	7.42 7.27
Ph	**10**	Ethyl vinyl ether	**16**	OEt	0.1	56	236.5	$C_{22}H_{21}ClN_2O_6$	59.39 59.01	4.76 4.65	6.30 6.00

(a) Unless otherwise indicated previous decomposition was observed for all melting points. (b) The upper percentage of the pair is always the Calculated and the bottom the Found. (c) Yield of mixture of both isomers. (d) Less-soluble isomer. (e) More-soluble isomer. (f) This experiment was carried out with the bromide rather than the perchlorate salt.

TABLE II

Rate Constants for the Addition of Styrene to Perchlorate Salts of Acridizinium Analogs at 65°

Formula	Name	k x 10^2 min^{-1}
1	Acridizinium	0.52
8	2-Azaacridizinium Oxide	3.7
9	3-Methyl-2-Azaacridizinium Oxide	2.9
10	3-Phenyl-2-Azaacridizinium Oxide	2.3
17	3-Phenyl-2-Azaacridizinium	0.58

and 395 (4.00). It was converted to the perchlorate for analysis and crystallized from methanol, m.p. >300°.

Anal. Calcd. for $C_{23}H_{17}ClN_2O_4$: C, 65.64; H, 4.07; N, 6.66. Found: C, 65.70; H, 4.20; N, 6.55.

2-Phenyl-1-(3-trifluoromethylphenyl)-1*H*-imidazo[1,2-*b*]isoquinolin-4-ium Bromide (**4**).

The preparation was carried out essentially as in the preparation of **3** except that *m*-trifluoromethylaniline was used in place of aniline and the reaction was continued for 24 hours. The bromide crystallized from methanol-ethyl acetate as fluorescent yellow crystals, m.p. 300°, yield 38%; uv max (abs. ethanol) 280 mμ (log ε 5.37), 375 (5.00) and 393 (5.02).

Anal. Calcd. for $C_{24}H_{16}BrF_3N_2$: C, 61.42; H, 3.44; N, 5.97; Br, 17.03. Found: C, 61.47; H, 3.35; N, 5.93; Br, 16.99.

5,10,12,13-Tetrahydro-1,2-diphenyl-11*H*-5,10-*endo*-cyclopent-1*H*-imidazo[1,2-*b*]isoquinolin-4-ium Bromide (**5**).

To a mixture of 36 ml. of anhydrous acetonitrile and 12 ml. of anhydrous methanol, 0.25 g. (3.8 mmoles) of freshly distilled cyclopentadiene and 0.3 g. (0.71 mmoles) of **3** was added. The mixture was stirred and heated at 65° for 12 hours by which time the long wavelength uv absorption had disappeared. The mixture was concentrated in a vacuum evaporator and the residue dissolved in water and washed with ether to remove excess cyclopentadiene or its dimer and sodium perchlorate added to the aqueous solution. The resulting precipitate was recrystallized from methanol, affording 0.1 g. (29%) of colorless needles, m.p. 241-242°.

Anal. Calcd. for $C_{28}H_{23}ClN_2O_4$: C, 69.06; H, 4.76; N, 5.75 Found: C, 69.25; H, 4.87; N, 5.81.

11-Carbazol-9-yl-5,10-dihydro-1-(3-trifluomethylphenyl)-2-phenyl-5,10-ethano-1*H*-imidazo[1,2-*b*]isoquinolin-4-ium Bromide (**6**).

To a mixture of 8 ml. of methanol and 16 ml. of acetonitrile, 0.3 g. (0.64 mmoles) of **4** and 0.59 g. (3.1 mmoles) of 9-vinylcarbazole were added. The mixture was stirred and heated at 50° for 10 hours. After 90% of the solvent had been removed using a vacuum evaporator, the residue was poured into ether. The resulting colorless precipitate was recrystallized from acetonitrile affording 0.1 g. (24%) of colorless crystals m.p. 252-254° dec.

Anal. Calcd. for $C_{38}H_{27}BrF_3N_3$: C, 68.88; H, 4.11; N, 6.34. Found: C, 68.74; H, 4.06; N, 6.13.

Pyrazino[1,2-*b*]isoquinolin-5-ium 2-Oxide Perchlorate (**8**).

A solution of 8.6 g. (50 mmoles) of 3-oximidomethylisoquinoline (**12**) in 60 g. of warm dimethylformamide was diluted with 80 g. of sulfolane, the mixture cooled to 20°, and 6.0 g. (64 mmoles) of chloroacetaldehyde oxime (**13**) was added. The resulting mixture was allowed to stand in the dark at room temperature for 14 days. The solid (4.0 g.) was collected and washed with ethyl acetate. Addition of ethyl acetate to the filtrate precipitated an additional 1.0 g. This material was suitable for cyclization but appeared to consist of two crystalline forms and was not obtained as analytically pure **7**(R = H, Z = NOH).

The 5 g. of solid was dissolved in 50 ml. of 6 *N* hydrochloric acid and the mixture heated at 100° for ten minutes. The mixture was poured into 150 ml. of cold water and excess sodium perchlorate was added. The yellow precipitate was collected, washed with cold water and dried affording 5.2 g. (35%) of yellow powder. The analytical sample, m.p. 200° dec. was crystallized from acetonitrile-ether; uv max (acetonitrile) 250 mμ (log ε 4.43), 280 (4.41), 300 (4.29), 312 (4.24) and 373 (4.10).

Anal. Calcd. for $C_{12}H_9ClN_2O_5$: C, 48.58; H, 3.06; N, 9.44. Found: C, 48.88; H, 2.94; N, 9.12.

3-Methylpyrazino[1,2-*b*]isoquinolin-5-ium 2-Oxide Perchlorate (**9**).

The perchlorate m.p. 199.5-200° dec. was prepared by addition of sodium perchlorate to a solution of the known (8) bromide and was crystallized from acetonitrile-ether; uv max (95% ethanol) 250 mμ (log ε 4.38), 265 (4.31), 300 (4.25), 312 (4.14), 370 sh (3.89), 386 (3.95), 412 (3.84).

Anal. Calcd. for $C_{13}H_{11}ClN_2O_5 \cdot 0.5H_2O$: C, 48.84; H, 3.78; N, 8.76. Found: C, 48.52; H, 3.44; N, 8.69.

2-Phenacyl-3-oximidomethylisoquinolinium Perchlorate (**7**, R = Ph, Z = O).

A solution of 4.3 g. (25 mmoles) of 3-oximidomethylisoquinoline (12) and 10 g. (50 mmoles) of phenacyl bromide in 200 ml. of pure acetone was refluxed for 36 hours affording 4.2 g. of the bromide salt suitable for cyclization. The perchlorate was prepared for analysis by crystallization from acetonitrile-ether, m.p. 165-175° dec.

Anal. Calcd. for $C_{18}H_{15}ClN_2O_6$: C, 55.32; H, 3.87; N, 7.17. Found: C, 55.31; H, 3.91; N, 7.05.

3-Phenylpyrazino[1,2-*b*]isoquinolin-5-ium 2-Oxide Perchlorate (**10**).

One gram (2.7 mmoles) of the crude bromide salt (**7**, R = Ph, Z = O) was dissolved in hot methanol, 2 ml. of 35% perchloric acid added (safety shield), the mixture heated at 60° on a water bath for 5 minutes, and then cooled in ice. The yellow product was collected and recrystallized from acetonitrile-ether affording 0.9 g. (80%) of product, m.p. 265° dec. uv max (acetonitrile), 242 mμ (log ε 4.63), 250 (4.68), 260 (4.57), 282 (4.43); 315 (4.47), 375 (3.99), 407 (3.76), 430 sh (3.62).

Anal. Calcd. for $C_{18}H_{13}ClN_2O_5$: C, 57.99; H, 3.51; N, 7.52. Found: C, 57.85; H, 3.26; N, 7.23.

Cycloaddition Reactions of Pyrazino[1,2-*b*]isoquinolin-5-ium 2-Oxide Perchlorate Salts (**8-10**).

The cycloaddition reactions were carried out by dissolving 0.3 g. of the aromatic salt (**8-10**) in 50 ml. of anhydrous acetonitrile (except in the 9-vinylcarbazole reactions where 1:1 acetonitrile-U.S.P. methanol was used to reduce polymerization) and adding an excess (2-8 molar) of the alkene. The mixture was allowed to stand at room temperature and the progress of the cycloaddition was followed by observing the disappearance of long wavelength (400-350 mμ) uv absorptions of aliquots. At the end of the indicated period, (Table I) the mixture was poured into 500 ml. of anhydrous ether and the resulting precipitate recrystallized from acetonitrile-ether.

3-Phenylpyrazino[1,2-*b*]isoquinolin-5-ium Bromide (**17**, R = Ph).

One-half g. (1.4 mmoles) of finely powdered 3-phenylpyrazino-[1,2-*b*]isoquinolin-5-ium-2-oxide bromide (**10**) was mixed with 5 ml. (52 mmoles) of phosphorus tribromide and the mixture refluxed and mechanically stirred rapidly for 20 minutes. The mixture was cooled and the product collected and washed with dry ether. Recrystallization of the product from methanol-ether yielded 0.25 g. (55%) of a brown salt m.p. 280-281° dec.; uv max (acetonitrile) 309 mμ (log ε 4.46), 375 sh (4.15), 390 (4.24).

Anal. Calcd. for $C_{18}H_{13}BrN_2$: C, 64.11; H, 3.88; N, 8.31. Found: C, 63.82; H, 3.95; N, 8.07.

The *perchlorate* salt, m.p. 279-280°, was crystallized from acetonitrile-ether.

Anal. Calcd. for $C_{18}H_{13}ClN_2O_4$: C, 60.60; H, 3.67; N, 7.85. Found: C, 61.15; H, 3.64; N, 7.74.

12-(2-Pyrrolidinone-1-yl)-6,11-ethano-6,11-dihydro-3-phenylpyrazino[1,2-*b*]isoquinolin-5-ium Perchlorate.

In the same manner used for the preparation of the corresponding oxide (**16**, Y = 2-pyrrolidone-1-yl), 0.08 g. of **17**, (R = Ph) perchlorate was treated with 1-vinyl-2-pyrrolidinone at room temperature for 2 hours to afford 0.1 g. (95%) of colorless crystals, m.p. 178-179° after recrystallization from acetonitrile-ether.

Anal. Calcd. for $C_{24}H_{22}ClN_3O_5$: C, 61.60; H, 4.74; N, 8.98. Found: C, 61.79; H, 4.83; N, 8.88.

Reaction Rates.

The reaction rates were measured in dimethyl sulfoxide at 65° using the technique described earlier (14) except that the aliquot was diluted with anhydrous acetonitrile to avoid the decomposition of the alkenophile by ethanol or water. Good pseudo first order rate constants were obtained.

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