Rearrangement of Tetrazole Ethers With Iodide Ions (1)

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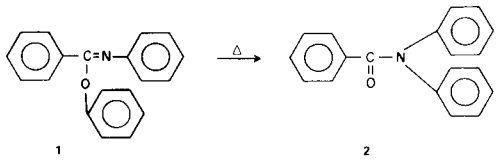
O to *N* Alkyl migration in 1-aryl-5-alkoxytetrazoles was observed on heating the substrates in the presence of sodium iodide. Unlike in similar rearrangements, methyl transfer did not occur in the presence of methyl iodide alone. Solvent effects were also investigated.

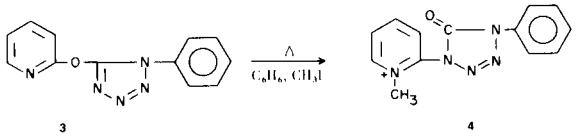
Introduction.

1,3-Alkyl or aryl migrations from oxygen to nitrogen have been known for some time. The thermal rearrangement of phenyl *N*-phenylbenzimidate (**1**) and related compounds to the respective amides **2** (Chapman rearrangement) and the migrations of alkyl groups in alkylimidates catalyzed by alkyl halides or sulfates (Lander rearrangement) have been reviewed (2). The application of this rearrangement to heterocycles such as pyrimidines has been referred to as the Hilbert-Johnson reaction (3).



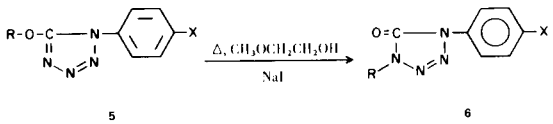
1 **2**

Recently a rearrangement of the tetrazolyl ether **3** to the pyridinium salt **4** has been reported (4):



3 **4**

We wish to report that methyl and benzyl tetrazolyl ethers **5** will undergo a similar 1,3-shift of the alkyl group in the presence of iodide ions to give the corresponding 1-aryl-4-alkyl-5-tetrazolones (**6**).

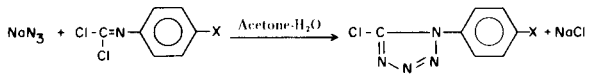


5 **6**

Preparation.

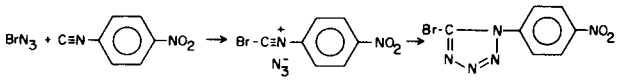
The tetrazolyl ethers **5** were prepared from the 1-aryl-5-halotetrazoles **8** or **10** and sodium alkoxides in good yields (Table I).

Substituted 1-phenyl-5-chlorotetrazoles (**8**) are accessible from *N*-aryldichloroazomethines **7** and sodium azide (5):



7 **8**

Utilizing the electrophilic property of XN_3 toward multiple bonds (6) we developed an alternative route to 5-halotetrazoles, namely by addition of chlorine or bromine azide to an aryl isocyanide (*eg.* **9**). The reaction presumably proceeds *via* a nitrilium ion intermediate, which rapidly reacts with azide ion, followed by ring closure to **10** (7).



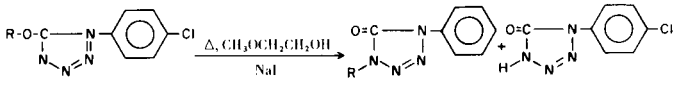
9 **10**

Rearrangement of Tetrazolyl Ethers.

The conversion of **5** to **6** with sodium iodide was studied in 2-methoxyethanol and dimethylformamide (DMF) as solvent systems.

A. In 2-Methoxyethanol.

When **5a** or **5b** was refluxed with sodium iodide (4:1 to 1:1 molar ratios) in 2-methoxyethanol at *ca.* 125° for 1 hour tetrazolone **6a** or **6b** was isolated in 70-80% yield together with 5-10% of 1-*p*-chlorophenyl-5-tetrazolone (**11**).

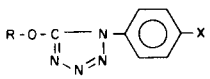


5a, R = CH_3
b, R = $C_6H_5CH_2$
c, R = $(CH_3)_2CH$

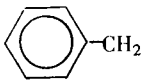
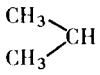
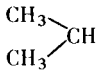
6a, R = CH_3 **11**
b, R = $C_6H_5CH_2$

TABLE I

Synthesis and Properties of 1-Aryltetrazolethers (**5**)



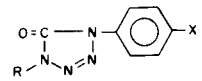
5

	R	X	τ (a) (ppm)	m.p.	Yield %	Formula	Calcd. % C	H	N	Found % C	H	N
a	CH_3	Cl	5.70	101-102	93	$C_8H_7ClN_4O$	45.67	3.35	26.60	45.74	3.26	26.46
b		Cl	4.35	107-108	85	$C_{14}H_{11}ClN_4O$	58.65	3.87	19.54	58.43	3.85	19.63
c		Cl		85-86	89	$C_{10}H_{11}ClN_4O$	50.32	4.64		50.47	4.78	
d	CH_3	H	5.67	72-73	92	$C_8H_8N_4O$	54.54	4.57	31.80	54.71	4.59	31.76
e	CH_3	NO_2	5.54	170-171	81	$C_8H_7N_5O_3$	43.44	3.19	31.66	43.25	3.18	31.69
f		NO_2		141-142	70	$C_{10}H_{11}N_5O_3$	48.19	4.44	28.10	48.24	4.48	28.14

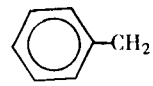
(a) Signal of methyl or benzyl protons.

TABLE II

Synthesis and Properties of 1-Aryl-4-alkyl-5-tetrazolones (**6**)



6

	R	X	τ (a) (ppm)	m.p.	Solvent Yield %	Formula	Calcd. % C	H	N	Found % C	H	N
6a	CH_3	Cl	6.34	103	DMF 84 MeOEtOH 71	$C_8H_7ClN_4O$	45.67	3.35	26.60	45.90	3.32	26.89
b		Cl	4.85	123-124	DMF 92 MeOEtOH 61	$C_{14}H_{11}ClN_4O$	58.65	3.87	19.54	58.70	3.76	19.53
c	CH_3	H	6.35	71-72	DMF 57 MeOEtOH 65	$C_8H_8N_4O$	54.54	4.57	31.80	54.56	4.61	31.99
d	CH_3	NO_2	6.25	171-172	DMF 89	$C_8H_7N_5O_3$	43.44	3.19	31.66	43.65	2.99	31.91

(a) Signal of methyl or benzyl hydrogens.

Most of the product **11** was extracted from the crude mixture as the water soluble sodium salt by washing with water. One recrystallization gave chromatographically pure **6**.

The rate of rearrangement was much slower when conducted in solvents of lower boiling points (ethanol, 2-butanone). In ethanol for example, **6** was usually contaminated by unreacted starting material and **11** became a major product (35 to 58%). We attribute the large increase in **11** to an interaction of the alkyl halide with the solvent (8), making the alkyl halide unavailable for the final alkylation step of **12** (see below.) No attempt

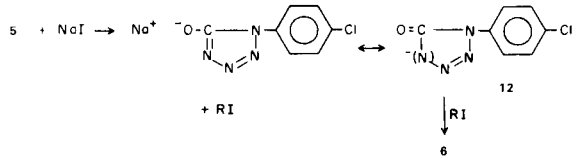
$$RI + R'OH \rightarrow R\text{-}O\text{-}R' + HI$$

was made to isolate any ethers that may have been formed.

Without iodide ions present, that is refluxing the ethers **5a** and **5b** in pure methoxyethanol, **5** was recovered unchanged with minor amounts of **11** and **6** detected by tlc.

A mechanism which would readily explain the role of iodide ion in the rearrangement is shown in Scheme I. The conversion is characterized by an overall gain in bond energies in the process C-O-C=N→ O=C-N. Scheme I,

SCHEME I



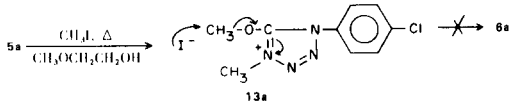
involving S_N2 attack by iodide at the iminoether alkyl with displacement of the resonance stabilized amidate **12** followed by alkylation on *N*, is supported by the following observations:

1. Alkylation of pure **12** with methyl iodide (or benzyl iodide) gave **6a** (or **6b**) in high yields. No *O*-alkylation products (**5a** or **5b**) were detected by tlc. (The presence of small quantities of a second alkylation product with the alkyl group attached to N-3 of the tetrazole ring will be discussed below).

2. An intramolecular mechanism is unlikely since the benzyl ether **5b** when heated with sodium iodide and methyl iodide produced mixtures of **6a** and **6b**. Such a result would be expected if there is competition between methyl iodide and benzyl iodide both attacking the nucleophilic N-4 of the ring:

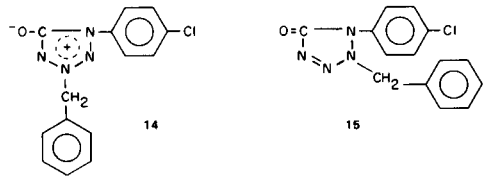
$$\mathbf{5b} \xrightarrow[\text{NaI}]{CH_3I} (\mathbf{12} + PhCH_2I) \xrightarrow{CH_3I} \mathbf{6a} + \mathbf{6b}$$

3. A rearrangement following the Lander mechanism (alkylation of **5** on N-4 followed by displacement at the alkyl ether as depicted by **13a** is also unlikely since refluxing of **5a** with methyl iodide in methoxyethanol did not result in formation of **6a**.

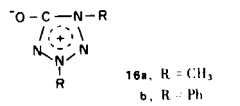


4. The more hindered isopropyl ether **5c** did not undergo isopropyl migration from *O* to *N*, on heating with sodium iodide, as would be expected if an S_N2 pathway is at work.

Tlc analysis of the alkylation product of pure **12** with benzyl iodide indicated, in addition to **6b** the presence of a new substance with an Rf value much lower than that of **6b**. It was nearly insoluble in benzene and was isolated pure in 4-5% yield by preparative thin layer chromatography and column chromatography. Elemental analysis and nmr were in accord with a structure isomeric to **6b**. The nmr spectrum closely resembles that of **6b** but the benzyl methylene hydrogens appeared farther downfield (τ4.52 vs. 4.85 for **6b**). An intensive carbonyl band in the ir was observed at 1680 cm^{-1} vs. 1710-1720 cm^{-1} for **6b**, and two bands were present in the uv max at 295 nm (ϵ 4,600) and 223 nm (ϵ 3,900). The mesoionic structure **14** is compatible with these data and appears more plausible than **15** which should have solubility and spectral properties closely resembling those of **6b**.



Mesoionic tetrazole derivatives have been reported before. Horwitz *et al.* (9) reported that methylation of 1-methyl-5-tetrazolone with diazomethane gave 1,4-dimethyl-5-tetrazolone (C=O at 1710 cm^{-1}) and a very small amount of material which they considered to be 1,3-dimethyl-5-tetrazolone **16a** having a carbonyl absorption at 1673 cm^{-1}. A 1,3-diphenyl-5-tetrazolone (**16b**) has been described by Farrar (10). The uv showed three peaks at 325, 261 and 225 nm and the C=O absorption appeared at 1695 cm^{-1}. Other mesoionic tetrazoles are known



(11). The isolation of **14** made it possible to reexamine whether it was also a byproduct of the rearrangement of **5** in methoxyethanol or DMF. Tlc clearly confirmed that **14** was formed in small quantities in both solvent systems. During the rearrangement of **5a** traces of an unknown substance, presumably a methyl analog of **14**, was detected by tlc but it was not isolated.

B. In DMF.

Rearrangement of the tetrazolyl ethers by sodium iodide occurs even more smoothly in refluxing DMF than in the alcohol solvents. The tetrazolones **6a** and **6b** were obtained in yields of 84-92% (Table II). The reaction is complete within less than 30 minutes even if the iodide/substrate ratio is reduced to 0.1:1.0, but usually a mole ratio of 3:1 was used. Tlc showed the presence of traces of **14** which could easily be removed by one recrystallization of the product. Even at lower temperatures (90° and 100°) all of **5a** or **5b** had reacted within one hour. However the product was contaminated by small amounts

of **11** as well as **14**. The slightly enhanced reactivity of **5** toward iodide ions in DMF is attributable to the higher polarity of this solvent *vs.* methoxyethanol.

Refluxing of **5b** in DMF with sodium iodide and methyl iodide produced a mixture of 61% **6a** and 39% **6b** based on nmr analysis of the methyl and methylene hydrogens and again pointing to an intermolecular reaction with **12** as an intermediate.

C. Thermal Rearrangement of Tetrazolyl Ethers in DMF.

In refluxing DMF the ethers **5a** and **5b** underwent a complete thermal rearrangement to **6a** or **6b** in the absence of iodide. This is in striking contrast to the reaction in methoxyethanol. Possibly traces of a nucleophile become more effective in the more polar solvent. However, this thermal conversion resulted in less pure products than when iodide was present; the products always contained **11** as well as other impurities. Tlc of the product obtained from **5b** showed four spots two of them corresponding to **11** and **14** (12).

D. Thermal Rearrangement of Tetrazolyl Ethers (Neat).

Some of the tetrazolyl ethers also underwent a Chapman type rearrangement on heating of the pure solid above its melting point. Thus, at 105° **5a** and **5b** gradually rearranged to **6a** and **6b** as the major products.

EXPERIMENTAL

Microanalyses were performed by Galbraith Laboratories, Knoxville, Tennessee. Melting and boiling points are uncorrected. Instrumental data were obtained from a Perkin Elmer Model 700 infrared spectrometer, a Bausch & Lomb Spectronic 505 ultraviolet spectrometer and a Varian T-60 nuclear magnetic resonance spectrometer with tetramethylsilane as an internal standard.

1-*p*-Chlorophenyl-5-chlorotetrazole (**8**).

The procedure by Maggiulli and Paine (5) was modified as follows: A solution of 21.06 g. (0.324 mole) of sodium azide in 110 ml. of water was added to a mixture of 67.5 g. (0.324 mole) of *p*-chlorophenylisocyanide dichloride (13) in 230 ml. of acetone which was stirred vigorously in an ice bath. After 5 minutes the cooling bath was removed and the mixture was refluxed for 75 minutes. Upon cooling, the organic layer was separated, the acetone was distilled off at reduced pressure, and the remaining oil was dissolved in benzene, washed twice with water and dried over anhydrous sodium sulfate. Removal of the benzene *in vacuo* gave an oil which crystallized on standing. After addition of cyclohexane the slurry of crystals was filtered off, washed with more cyclohexane and dried: 59.9 g. (85.9%), m.p. 74-75° (lit. (5) 70-72°). Recrystallization from chloroform/*n*-pentane did not change the melting point.

1-*p*-Nitrophenyl-5-bromotetrazole (**10**).

A mixture of 19.5 g. (0.30 mole) of sodium azide, finely powdered, 125 ml. of dichloromethane and 12 ml. of water was stirred in a 500 ml. Morton type three necked flask in an ice water bath for ten minutes. Bromine, 9.6 g. (0.060 mole) was added in portions. Stirring was continued for thirty minutes. The dichloromethane phase was decanted, the aqueous residue was washed twice with methylene chloride and the combined organic solutions containing BrN_3 were dried over anhydrous magnesium sulfate, filtered through glass wool and added under ice cooling to a solution of 3.9 g. (0.0263 mole) of *p*-nitrophenylisocyanide (14) in 35 ml. of dichloromethane. The solvent was evaporated and 6.89 g. of the yellow crude product was washed with Skellysolve B and recrystallized from chloroform/Skellysolve B: 6.0 g. (84%), m.p. 120° dec.

Anal. Calcd. for $C_7H_4BrN_5O_2$: C,31.13; H,1.49. Found C,31.25; H,1.57.

1-Aryl-5-alkoxytetrazoles (**5**).

1-*p*-Chlorophenyl-5-benzyloxytetrazole (**5b**).

Sodium (1.15 g., 0.05 mole) was dissolved in 40 ml. of redistilled benzyl alcohol at 100-120° under a nitrogen blanket. After cooling of the solution to room temperature, 10.75 g. (0.05 mole) of 1-*p*-chlorophenyl-5-chlorotetrazole (**8**) in 30 ml. of benzyl alcohol was added rapidly with cooling. The mixture was then kept at 80° for 2 hours under nitrogen. The cooled solution was diluted with an excess of benzene, washed three times with water and dried over sodium sulfate. Benzene was removed in a rotary evaporator and the benzyl alcohol distilled off at a pressure of 1 mm Hg (b.p. 65°). The residual oil crystallized and was washed with cyclohexane: 13.5 g., m.p. 106-107°; recrystallization from chloroform/Skellysolve B: 12.2 g. (85%), m.p. 107-108°; nmr (deuteriochloroform): τ 4.35 (s, 2H), 2.6-2.2 (m, 9H); ir (potassium bromide): 1595, 1550, 1495, 1440, 1400, 1340, 1300, 1295, 1270, 1240, 1210, 1130, 1090, 1040, 1010, 985, 932, 915, 830, 765, 753, 730, 695 cm^{-1}.

The methyl, ethyl and isopropyl tetrazole ethers listed in Table I were prepared similarly except that the reaction mixture was refluxed for one hour with the respective alcohol. The excess alcohol was then removed by vacuum distillation, the crystalline residue was washed with water, dried and recrystallized from aqueous methanol, ethanol or benzene/hexane. The purity of the compounds was confirmed by tlc (Silica Gel F-254, Precoated, plates 5 x 10 cm, E. Merck) development with benzene/ethanol (95:5 v/v). Tetrazole **5a** should be stored in the refrigerator because at room temperature it gradually rearranges to **6a**. All tetrazole ethers showed a strong absorption band at 1550-1570 cm^{-1}.

Rearrangement of Tetrazolyl Ethers **5** with Sodium Iodide to **6**.

The following examples are representative of the transformations **5** → **6** (see Table II) in methoxyethanol or dimethylformamide. In the other solvents examined (ethanol, 2-ethoxyethanol, 2-butanone and diglyme) lower yields of **6** were obtained while the yield of **11** and other impurities increased.

Methoxyethanol as Solvent.

(a) 1-*p*-Chlorophenyl-4-methyl-5-tetrazolone (**6a**).

To a solution of 0.421 g. (0.0020 mole) of 1-*p*-chlorophenyl-5-methoxytetrazole (**5a**) in 10 ml. of distilled methoxyethanol was added 1.2 g. (0.0080 mole) of sodium iodide. After one hour of reflux the solvent was removed *in vacuo*. The residue was washed with water and dried: 0.302 g. (71%), m.p. 101-102°. The analytical sample was recrystallized from aqueous (50%) ethanol: m.p. 103°; nmr (deuteriochloroform): τ 6.35 (s, 3H) 2.7-2.1 (m, 4H); ir (potassium bromide): 1720, 1490, 1420, 1390, 1360, 1280, 1145, 1100, 1050, 1020, 840, 810, 740, 710 cm^{-1}.

Acidification of the filtrate with dilute hydrochloric acid gave a crystalline precipitate, 0.024 g. (6%) of 1-*p*-chlorophenyl-5-

tetrazolone (**11**), m.p. 201-205° dec., recrystallized from aqueous ethanol, m.p. 207-208° dec., (lit. (15) m.p. 206-207° dec.): ir (potassium bromide): C=O 1720 cm^{-1}. (b) Refluxing 1.05 g. (0.005 mole) of **5a** in 25 ml. of methoxyethanol for 70 minutes without sodium iodide and workup as above gave 1.0 g. of **5a**, m.p. 98-99.5°; **6a** (and **11**) was detected as a slight impurity by tlc. Similar results (92% recovery) were obtained on refluxing **5a** with 4 equivalents of methyl iodide in methoxyethanol for 60 minutes.

(c) 1-*p*-Chlorophenyl-5-isopropoxytetrazole (**5c**). This compound treated as in (a) was recovered in 70% yield together with 16% of **11**.

(d) Reaction of **5b** with sodium iodide and methyl iodide. A solution of 0.572 g. (0.002 mole) of **5b**, 1.2 g. (0.008 mole) of sodium iodide and 0.13 ml. of (0.002 mole) of methyl iodide in 10.0 ml. of methoxyethanol was refluxed for one hour. After evaporation of the solvent at reduced pressure the oily residue was diluted with water. The crystalline precipitate was filtered, washed with water and dried: 0.491 g., m.p. 60-93°. Tlc showed the presence of two strong spots corresponding to **6a** and **6b** and two very weak spots corresponding to **11** and **14**; nmr integration gave this composition: **6a**, 54.5%, **6b**, 44%, **14**, 1.5%.

DMF as Solvent.

(a) To a solution of 0.421 g. (0.002 mole) of 1-*p*-chlorophenyl-5-methoxytetrazole (**5a**) in 10.0 ml. of DMF, 0.90 g. (0.0060 mole) of sodium iodide was added and the mixture was refluxed for 1 hour. The solvent was distilled *in vacuo*, the yellowish oil diluted with water and the colorless precipitate of **6a** was filtered, washed with water and dried: 0.354 g. (84%), m.p. 101-102°. Addition of dilute hydrochloric acid to the filtrate gave no precipitate. The other tetrazolones listed in Table II were prepared similarly.

(b) Rearrangement of Tetrazolyl Ethers at Lower Temperatures.

1. Reaction of **5b** with Sodium Iodide at 100°.

A solution of 0.573 g. (0.002 mole) of **5b** and 0.90 g. of sodium iodide in 10 ml. of DMF was kept at 100° for one hour. After removal of the solvent 0.536 g. of **6b** was isolated, m.p. 117-120°. The presence of small amounts of **11** and **14** was evident from tlc and nmr.

2. Reaction of **5b** Without Sodium Iodide at 100°.

In the absence of sodium iodide but under otherwise identical conditions as under 1, 0.472 g. of a product, m.p. 85-91°, was isolated. Tlc showed two main spots due to **5b** and **6b** and two small ones of **11** and **14**. Nmr analysis showed that unreacted **5b** accounted for 61%, **6b** for 39%.

(c) Rearrangement of **5b** with Sodium Iodide in the Presence of Methyl Iodide.

To a solution of 0.573 g. (0.002 mole) of 1-*p*-chlorophenyl-5-benzyloxytetrazole (**5b**) in 10.0 ml. of DMF containing 0.60 g. (0.004 mole) of sodium iodide was added 0.13 ml. (0.002 mole) of methyl iodide and the mixture was refluxed for 45 minutes. After removal of the solvent water was added and the precipitate was filtered, washed with water and dried: 0.522 g. Tlc indicated a mixture of **6a** and **6b**, in a ratio of 61:39 by nmr integration.

Alkylation of **12**.

1-*p*-Chlorophenyl-5-tetrazolone (**11**) was obtained by saponification of 1-*p*-chlorophenyl-5-chlorotetrazole (**8**) with sodium hydroxide solution at 70° followed by acidification with dilute hydrochloric acid. The compound was recrystallized from 50% (v/v) aqueous ethanol: 97% yield, m.p. 208° dec.

The sodium salt **12** was prepared by heating equivalent amounts of **11** with sodium carbonate in water. The solution was filtered, water was distilled off and the crystalline residue was dried at 80° over phosphorus pentoxide *in vacuo*, 94% yield.

(a) Alkylation of **12** with Benzyl Iodide.

A solution of 0.454 g. (0.0021 mole) of benzyl iodide, 0.437 g. (0.002 mole) of **12** in 10 ml. of 2-methoxyethanol was refluxed for one hour. After removal of the solvent at reduced pressure the residue was treated with water and dried: 0.522 g., m.p. 115-117°. Tlc shows complete absence of **5b**. The main product was **6b**. Small amounts of **11** and a new substance, **14**, was also detected (spots of **14** on the tlc plate showed a bluish fluorescence in the uv light). After extraction of **11** with dilute sodium hydroxide solution, the product (m.p. 117-120°) consisted of **6b** and **14** (9% of **14** by nmr). Separation of 15 mg. of **14** from 400 mg. of the mixture was achieved by preparative thin layer chromatography. The R_f of **14** in benzene/ethanol (95:5) was much lower than that of **6b**. (0.34 vs. 0.91).

The two compounds **6b** and **14** can be separated more conveniently using column chromatography. A column was filled with a slurry of 50 g. of silica gel (0.2-0.5 mm, E. Merck) in benzene and 1 g. of the mixture in 4 ml. of benzene was added. **6b** was eluted with benzene (200 ml.). The remaining **14** was removed from the column with 95% ethanol and was obtained in a yield of 5%. Recrystallization from aqueous ethanol, m.p. 119°; nmr (deuteriochloroform): τ 4.52 (s, 2H), 2.7-1.9 (m, 9H); ir (potassium bromide): 1680, 1580, 1485, 1430, 1410, 1360, 1325, 1305, 1240, 1210, 1185, 1090, 1060, 1010, 840, 710 cm^{-1}; λ max (0.005% in ethanol): 223 nm (ϵ 3900) and 295 nm (ϵ 4600).

Anal. Calcd. for $C_{14}H_{11}ClN_4O$: C, 58.65; H, 3.87; N, 19.54. Found C, 58.38; H, 3.90; N, 19.73.

(b) Alkylation of **12** With Methyl Iodide.

A solution of 0.437 g. (0.0020 mole) of **12** and 0.15 ml. (0.0024 mole) of methyl iodide in 10.0 ml. of methoxyethanol was treated as in (a) to furnish 0.369 g. of nearly pure **6a**, m.p. 102-103°. Tlc indicated only traces of an impurity possibly related to **14**.

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