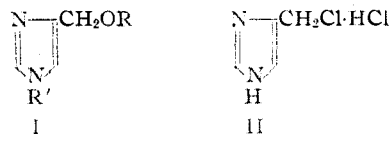
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, SYRACUSE UNIVERSITY]

Ethers of 4(5)-Hydroxymethylimidazole[1,2]

BY P. M. RUOFF AND R. C. SCOTT[3]

With the increasing interest in ethers of the general formula, $RO(C)_nNR_2$, as antihistaminic agents,[4] attention was directed in this laboratory toward the ethers of 4(5)-hydroxymethylimidazole (I) where R = alkyl or aryl and R′ = H or alkyl. There have been a few reports in the



I II

literature on the preparation, or attempted preparation, of ethers of this type. Pyman[5] prepared 4(5)-ethoxymethylimidazole unexpectedly by refluxing 4(5)-chloromethylimidazole hydrochloride (II) with potassium cyanide in ethyl alcohol. Saikachi[6] condensed II in a Williamson synthesis with *p*-hydroxyphenylethylamine, diethylaminoethanol and *p*-nitrothiophenol. The ethers were obtained in low yields as chloroplatinates. After our work was completed Turner, Huebner and Scholz[7] stated that in an effort to prepare ethers by treating (II) with sodium alkoxides they obtained only resinous substances. They suggested that the highly active chloroamine liberated from its hydrochloride (II) by the alkoxide rapidly self condensed.

This paper describes the syntheses of ten ethers of the type I in which R′ = H and R = alkyl or aryl (Table I). Attempts to prepare the benzyl, *t*-butyl, *β*-dimethylaminoethyl and benzhydryl ethers have led to inconclusive results thus far.

The aromatic ethers (I, R′ = H, R = aryl) were prepared by the Williamson method using II and two equivalents of the corresponding sodium phenolate in ethanol solution. The aliphatic ethers, on the other hand (I, R′ = H, R = alkyl) were prepared by heating II on the steam-bath with a large excess of the absolute alcohol for fifty to one hundred hours. In the presence of anhydrous bicarbonate the reaction time could be cut to seven to fifteen hours. The Williamson method using II and two equivalents of the sodium alcoholate in this series failed to produce any ethers[7] but gave products whose derivatives, that is, the oxalates and picrates, exhibited the properties of polymeric substances such as wide melting range, insolubility in common solvents, and failure to give X-ray diffraction patterns.

This failure of the Williamson synthesis in the aliphatic series and success in the aromatic series may be due to the acidity of the imino hydrogen.[7] It may be predicted that imidazole would be more acidic than pyrrole since its ion would be more stable.[8] This greater stability may be attributed to the location of the negative charge on the nitrogen in two of the five resonant forms of the imidazole ion whereas in the pyrrole ion the negative charge falls on nitrogen in only one of the resonating forms.[9]

Since pyrrole and the aliphatic alcohols[10] have a *pKa* ranging from 19 to 16, chloromethylimidazole need not be much more acidic than pyrrole to neutralize the sodium alcoholate and thus react with itself. On the other hand, it might be expected that the chloromethylimidazole would react with the sodium phenolates to give ethers or to react with the sodio derivatives of acetoacetic ester and malonic ester,[11] cases in which the *pKa* values may range from 11 to 10.[12]

Table I lists the ethers and their salts prepared in our study thus far. Further work is in progress in preparing ethers of the type I in which R′ = CH_3 and R = alkyl and aryl.

When the Williamson reaction was attempted using the sodio derivative of 4(5)-hydroxymethylimidazole (I, R = R′ = H) and an alkyl halide such as methyl iodide, N-alkylation resulted giving two N-alkyl products (III and IV).[13] Since 4-hydroxymethyl-1-methylimidazole (III) is a new compound, its structure was established by reducing it with red phosphorus and hydriodic acid to the known 1,4-dimethylimidazole.[13] It is interesting to note that benzoylation (in the absence of base) of 4(5)-hydroxymethylimi-

(1) Taken from the thesis of R. C. Scott submitted in partial fulfillment of the requirement for the Ph.D. degree, July, 1949.

(2) Presented before the Organic Division of the ACS, Philadelphia Meeting, April 10, 1950.

(3) Bristol Laboratories, Inc., predoctoral fellow.

(4) Huttrer, *Ensymologia*, **12**, 277 (1948); see also Cheney, Smith and Binkley, THIS JOURNAL, **71**, 60 (1949).

(5) Pyman, *J. Chem. Soc.*, **99**, 678 (1911).

(6) Saikachī, *J. Chem. Soc. Japan*, **65**, 196 (1944).

(7) Turner, Huebner and Scholz, THIS JOURNAL, **71**, 2801 (1949). More recently these authors, *ibid.*, **71**, 3942 (1949), have prepared two 4-(2-aryloxyethyl)-imidazole types.

(8) See Branch and Calvin, "The Theory of Organic Chemistry," Prentice-Hall, Inc., New York, N. Y., 1945, pp. 266–267. Tetrazole is quoted as having a dissociation constant of the order of 10^{-5}. Albert, Goldacre and Phillips, *J. Chem. Soc.*, 2240 (1948), give the *pKa* of benzimidazole as approximately 12 while Benson and Savell, *Chem. Rev.*, **46**, 1 (1950), give the *pKa* of the *s*-triazoles as approximately 6.

(9) Substitution of the acidic hydrogen on the imidazole ring with a benzyl group which could be later removed might serve as the basis for a successful Williamson synthesis in the aliphatic series; see Jones, THIS JOURNAL, **71**, 383 (1949).

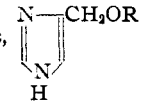
(10) McEwen, *ibid.*, **58**, 1124 (1936).

(11) Pyman, *J. Chem. Soc.*, **99**, 1386 (1911).

(12) Hammett, "Physical Organic Chemistry," McGraw-Hill Book Company, Inc., New York, N. Y., 1940, p. 244.

(13) Pyman, *J. Chem. Soc.*, **97**, 1820 (1910); **99**, 2179 (1911).

TABLE I

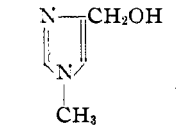
ETHERS OF 4(5)-HYDROXYMETHYLIMIDAZOLE, 

Procedure A. Excess alcohol, prolonged heating. Product obtained by distillation (<1 mm.)
Procedure B. Excess alcohol, prolonged heating. Product obtained as a salt.
Procedure C. Excess alcohol, prolonged heating. Product obtained by ether extraction.
Procedure D. Excess alcohol, in the presence of sodium bicarbonate.
Procedure E. Williamson method using II.

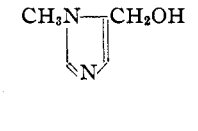
R	Method of preparation	Free base or salt	M. p.,[a] °C.	Yield, %	Purification solvent	Empirical formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
CH_3—	A	Free base	45–46	61		$C_5H_8ON_2$	53.59	53.64	7.14	7.20
		Picrate	97–98		Water[b]	$C_{11}H_{11}O_8N_5$	38.61	38.88	3.22	3.40
CH_3CH_2—	A	Free base	56[c]	70	[b]	$C_6H_{10}ON_2$	57.12	56.88	7.93	7.85
	B	Hydrochloride	83.5–84	75–86	Dry acetone	$C_6H_{11}ON_2Cl$	44.34	44.30	6.77	6.84
		Oxalate	166.5–167[c]	...	Ethanol	$C_8H_{12}O_5N_2$	46.53	46.90	5.94	5.86
		Picrate	111–112	57	Water	$C_{12}H_{13}O_8N_5$	40.56	40.60	3.66	3.69
$CH_3CH_2CH_2$—	A	Free base	43–44	57	[d]	$C_7H_{12}ON_2$				
		Hydrochloride	99–99.5	83	Dry acetone	$C_7H_{13}ON_2Cl$	47.62	47.60	7.38	7.50
		Picrate	111.5–112.5	...	Water	$C_{13}H_{15}O_8N_5$	42.29	42.26	4.06	4.13
$(CH_3)_2CH$—	A	Free base	30–40	52–55	[b,d]	$C_7H_{12}ON_2$	60.02	58.45	8.57	8.23
		Picrate	121–121.5	...	Water	$C_{13}H_{15}O_8N_5$	42.29	42.50	4.06	4.04
$CH_3CH_2CH_2CH_2$—	A, D	Free base	22–24	38, 38	[d]	$C_8H_{14}ON_2$				
		Picrate	82.5–83.5	...	Water	$C_{14}H_{17}O_8N_5$	43.88	43.80	4.44	4.30
$(CH_3)_2CHCH_2$—	C	Free base	21–23	82	[d]	$C_8H_{14}ON_2$				
		Picrate	107.5–108	...	Water	$C_{14}H_{17}O_8N_5$	43.88	43.82	4.44	4.73
C_6H_5	E	Free base	147–147.5	76	50% Ethanol	$C_{10}H_{10}ON_2$	68.85	69.11	5.75	5.91
		Picrate	135–136	...	50% Ethanol	$C_{16}H_{13}O_8N_5$	47.66	47.65	3.22	3.36
o-$CH_3C_6H_4$—	E	Hydrochloride	194–195	56	Ethanol	$C_{11}H_{13}ON_2Cl$	58.83	58.88	5.79	6.05
		Picrate	164–165	...	Ethanol	$C_{17}H_{15}O_8N_5$	48.94	48.90	3.55	3.72
p-$CH_3C_6H_4$—	E	Free base	139–140	85	50% Ethanol	$C_{11}H_{12}ON_2$	70.23	69.92	6.38	6.49
		Picrate	163–164	...	Water	$C_{17}H_{15}O_8N_5$	48.94	48.86	3.55	3.71
o-$C_6H_5CH_2C_6H_4$—	E	Hydrochloride	181–181.5	39	Ethanol	$C_{17}H_{17}ON_2Cl$	67.91	67.94	5.65	5.68
		Picrate	169.5–170.5	...	50% Ethanol	$C_{23}H_{19}O_8N_5$	56.00	56.18	3.85	3.94

[a] Melting points uncorrected unless otherwise stated. [b] Distillate analyzed without further purification. [c] Melting point corrected. Pyman[5] gives the corrected melting points of the free base and oxalate as 53–55° and 165–167°, respectively. [d] No suitable solvent was found for recrystallization.

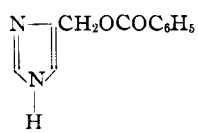
dazole, on the other hand, is reported to give the *o*-benzoyl compound, V.[14]



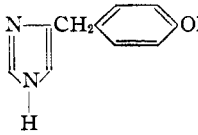
III



IV



V



VI

When an attempt was made to obtain the phenyl ether (I, R′ = H, R = C_6H_5) using II and a large excess of phenol, only 4(5)-hydroxymethylimidazole and *p*-4(5)-imidazolymethylphenol (VI) were isolated after working up the reaction mixture. The structure of VI was proved by methylation of VI followed by permanganate oxidation[15] of the resulting mixture of isomers to give *p*-methoxybenzoic acid in 40% yield.

(14) Pyman, *J. Chem Soc.*, **101**, 541 (1913).

(15) The instability of the imidazole ring to permanganate oxidation has been reported; see Pyman, *J. Chem. Dyers and Colorists*, **36**, 107 (1925); also, Pinner and Schwarz, *Ber.*, **35**, 2448 (1902).

Several of the compounds prepared have been submitted to the Bristol Laboratories, Syracuse, N. Y., for pharmacological testing. Results of these tests will be published when the series is completed.

Experimental

4(5)-Hydroxymethylimidazole.—The picrate[16] of this compound was prepared from both fructose[17] and sucrose.[18] The hydrochloride[16] was then prepared from the picrate but instead of purifying the product by recrystallization from ethanol, the hydrochloride was ground under dry acetone until the color was removed. The free base was prepared from the picrate using the method of Pyman.[5]

4(5)-Chloromethylimidazole Hydrochloride.[5]—The product was ground under dry acetone until most of the color was removed rather than recrystallized from ethanol.

4(5)-Methoxymethylimidazole (I, R = CH_3, R′ = H) **Procedure A.**—A typical example is as follows: A mixture of 4(5)-chloromethylimidazole hydrochloride (15.3 g., 0.10 mole) and 320 g. (10 mole) of absolute methyl alcohol was refluxed for ninety-eight hours on the steam-bath. After removal of the alcohol at reduced pressure, the resulting oil was treated with 100 ml. of water and 16.8 g. (0.20 mole) of sodium bicarbonate. Removal of the water at reduced pressure gave a gummy solid which was extracted with two 100-ml. portions of ethanol. Removal of the solvent at reduced pressure and distillation (< 1

(16) Totter and Darby, *Org. Syn.*, XXIV, 64 (1944); see also THIS JOURNAL, **64**, 463 (1942).

(17) We wish to thank Dr. R. F. Phillips of the Sugar Foundation for a generous gift of fructose.

(18) Albertson and Archer, THIS JOURNAL, **67**, 309 (1945).

mm.) of the resulting oil gave 6.8 g. (61%) of a viscous liquid which solidified upon standing in the refrigerator for three days; m. p. 45-46°. The compound was analyzed without further purification. Preparation of the picrate in the usual fashion gave 4(5)-methoxymethylimidazole picrate which was recrystallized from water; m. p. 97-98°.

4(5)-Ethoxymethylimidazole Hydrochloride (I, R = C_2H_5, R′ = H). **Procedure B.**—In general this procedure is typical. A solution of 6.13 g. (0.04 mole) of 4(5)-chloromethylimidazole hydrochloride in 184 g. (4.0 moles, 230 ml.) of absolute ethyl alcohol was refluxed on the steam-bath for seventy-two hours. Removal of excess alcohol at reduced pressure gave an oil which, when recrystallized from 60 ml. of dry acetone, gave 5.6 g. (86%) of 4(5)-ethoxymethylimidazole hydrochloride, m. p. 82.5-83.5°. Repeated recrystallizations from dry acetone gave a product with a constant melting point of 83.5-84°.

In the presence of 4 moles of dry sodium bicarbonate a 75% yield of 4(5)-ethoxymethylimidazole hydrochloride was obtained after refluxing the reaction mixture for seven hours. In this case sodium chloride and excess bicarbonate were removed by filtration and dry hydrogen chloride gas passed into the solution until no more gas was absorbed. Removal of the solvent at reduced pressure gave an oil which was recrystallized once from dry acetone; m. p. 80-81°.

4(5)-Isobutoxymethylimidazole (I, R = $(CH_3)_2CHCH_2$-, R′ = H). **Procedure C.**—A solution of 9.55 g. (0.0625 mole) of 4(5)-chloromethylimidazole hydrochloride in 462 g. (6.25 moles, 575 ml.) of absolute isobutyl alcohol was heated on the steam-bath for ninety hours. After the alcohol was removed under reduced pressure, the oil was dissolved in 50 ml. of water and 10 g. (0.12 mole) of sodium bicarbonate added. The basic solution was extracted with three 100-ml. portions of ether. After drying overnight over anhydrous magnesium sulfate, the ether solution was filtered and the ether distilled to yield 8.2 g. of a yellow-green oil (89%).

This oil (0.053 mole) dissolved in 15 ml. of absolute ethyl alcohol was added to a hot solution of 12.2 g. (0.053 mole) of picric acid in 120 ml. of absolute ethyl alcohol. After the alcohol was removed under reduced pressure, the resulting oil crystallized on cooling and scratching. The yield was 18.8 g. (82%); m. p. 98-100°.

The crude picrate was dissolved in 850 ml. of boiling water, filtered and cooled for six hours. The yellow crystals were filtered and air dried. This produced 13.8 g. (60%) of material; m. p. 107-108°. Concentration of the filtrate under reduced pressure gave 3.2 g. of material (14%); m. p. 105-108°. Recrystallization from water gave a melting point of 107.5 to 108°.

4(5)-Butoxymethylimidazole (I, R = $CH_3CH_2CH_2CH_2$-, R′ = H). **Procedure D.**—Ten grams (0.065 mole) of 4(5)-chloromethylimidazole hydrochloride was dissolved in 480 g. (6.5 moles, 600 ml.) of absolute *n*-butyl alcohol and 22.0 g. (0.26 mole) dry sodium bicarbonate added. The solution was heated on the steam-bath for fifteen hours with stirring, after which it was cooled and filtered. The alcohol was removed at reduced pressure and the resulting oil vacuum distilled (< 1 mm.). The yield was 3.8 g. (38%) of product which solidified on standing in the ice box; m. p. 22-24°. There was much decomposed material remaining in the distilling flask. The picrate prepared in the usual fashion was recrystallized from water; m. p. 82.5-83.5°.

4(5)-Phenoxymethylimidazole (I, R = C_6H_5, R′ = H). **Procedure E.**—The procedure is typical of the Williamson reaction for the preparation of the aromatic ethers.

To a solution of 1.84 g. (0.08 mole) of sodium in 150 ml. of ethanol was added 7.5 g. (0.08 mole) of phenol in 25 ml. of ethanol. After the solution was stirred for two and one-half hours and then cooled in an ice–hydrochloric acid bath, 6.1 g. (0.04 mole) of 4(5)-chloromethylimidazole hydrochloride in 50 ml. of ethanol was added with stirring over a period of twenty minutes. The mixture was then stirred at room temperature for six hours. The sodium chloride (4.5 g., 97%) was filtered off and the alcohol removed under reduced pressure. To the resulting oil was added 20 ml. of 6 *N* hydrochloric acid and 30 ml. of water. The solution was treated with 90 ml. of a saturated sodium bicarbonate solution after extraction with two 50-ml. portions of ether. The precipitate was filtered off and dried in a vacuum desiccator giving 5.3 g. of 4(5)-phenoxymethylimidazole (76%); m. p. 146-148°. The analytical sample was recrystallized from 50% ethanol; m. p. 147-147.5°. The picrate prepared in the usual fashion was recrystallized from 50% ethanol; m. p. 135-136°.

4- and 5-Hydroxymethyl-1-methylimidazole (III and IV).—After stirring a mixture of 13.4 g. (0.137 mole) of 4(5)-hydroxymethylimidazole and 3.15 g. (0.137 mole) of sodium in 250 ml. of absolute isopropyl alcohol for thirty-six hours there was added 19.4 g. (0.137 mole) of methyl iodide dissolved in 25 ml. of absolute isopropyl alcohol. The solution was stirred at room temperature for nine days. The alcohol was removed under reduced pressure and the resulting oil distilled (< 1 mm.) giving 9.1 g. (63%) of an oil which solidified on standing.

The picrates were prepared by the addition of a solution of 0.5 g. of (0.0045 mole) of the distillate to 1.0 g. (0.0045 mole) of picric acid in 20 ml. of absolute ethanol. The resulting precipitate was filtered immediately and air dried, fraction I, 1.1 g., m. p. 135-142°. The solution was allowed to stand twenty minutes and filtered giving 0.1 g. of a solid; fraction II, m. p. 160-161°. Fraction I was recrystallized from absolute ethanol: m. p. 153.5-154.5°.

Anal. Calcd. for $C_{11}H_{11}O_6N_5$: C, 38.72; H, 3.22. Found: C, 38.92; H, 3.35.

Fraction II was recrystallized from water; m. p. 163-164° (166-167° cor.). The melting point of the picrate of 5-hydroxymethyl-1-methylimidazole (IV) is reported as 166° (cor.).[19]

Anal. Calcd. for $C_{11}H_{11}O_8N_5$: C, 38.72; H, 3.22. Found: C, 38.90; H, 3.35.

Two mixtures of fractions I and II melted at 138-143° and 138-145°.

The remainder of the distillate was worked up in somewhat the same fashion to give ultimately 12.1 g. (46%) of fraction I, presumably the picrate of 4-hydroxymethyl-1-methylimidazole (III) and 3.4 g. (13%) of fraction II, 5-hydroxymethyl-1-methylimidazole picrate. Concentration at reduced pressure of all the alcoholic recrystallizations liquors gave 8.0 g. (31%) of a mixture of picrates.

1,4-Dimethylimidazole.—Fraction I was reduced with red phosphorus and hydriodic acid in the following manner. A mixture of 3.4 g. (0.01 mole) of fraction I, 75 ml. of benzene, and 40 ml. of 1 *N* hydrochloric acid was shaken at 60° until the picrate dissolved. The aqueous layer was extracted five times with 50-ml. portions of warm benzene, decolorized with charcoal, treated with 2.0 g. of sodium bicarbonate and then evaporated to dryness at reduced pressure. Extraction of the residue with two 15-ml. portions of absolute ethanol gave 0.6 g. (0.0054 mole) of a green oil after removal of the alcohol.

The green oil was heated in a sealed tube together with 0.15 g. (0.005 mole) of red phosphorus and 3 ml. of 47% hydriodic acid at 160° for five and a half hours. The reaction mixture was filtered, made basic with 6 *N* sodium hydroxide and filtered again. Extraction of the filtrate with several portions of chloroform followed by drying of the latter with potassium carbonate gave 0.35 g. (68%) of an oil after filtration and removal of the solvent.

The picrate was prepared in the usual fashion and recrystallized from water; m. p. 167-168° (cor.), Pyman[15] gives the melting point of 1,4-dimethylimidazole picrate as 167-168° (cor.).

Anal. Calcd. for $C_{11}H_{11}O_7N_5$: C, 40.63; H, 3.38. Found: C, 40.50; H, 3.44.

Attempts to prepare the oxalate gave a product whose melting point checked the literature[13] but whose analysis was unsatisfactory.

***p*-4(5)-Imidazolylmethylphenol** (VI).—After some preliminary work on smaller runs the following procedure was found suitable.

(19) Hubball and Pyman, *J. Chem. Soc.*, 28 (1928).

To 470 g. (5.0 moles) of phenol heated with stirring on the steam-bath was added 15.3 g. (0.10 mole) of 4(5)-chloromethylimidazole hydrochloride in five equal portions over a period of five hours. The solution was then heated on the steam-bath for sixty-five hours with stirring, cooled and extracted four times by vigorously stirring for two hours with 100 ml. of 2 *N* hydrochloric acid and separating. The combined extracts were treated with three 150-ml. portions of benzene and the water removed under reduced pressure giving 6.3 g. of an oil which was then dissolved in 60 ml. of absolute ethyl alcohol. To this was added 6.8 g. of picric acid dissolved in 110 ml. of absolute ethyl alcohol. The solution was evaporated to about one-sixth of its original volume, cooled and filtered giving 4.2 g. of material; m. p. 150–160°.

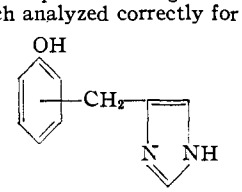
The filtrate was concentrated to one-half its volume, cooled and filtered; 0.6 g., m. p. 110–116°. Further evaporation of the filtrate gave an orange oil which could be crystallized from water; 2.6 g., m. p. 147–150°.

The entire process was repeated three times; that is, the extraction of the original reaction mixture with several portions of 2 *N* hydrochloric acid, the removal of the water, the conversion of the resulting oil to the picrate with an equivalent amount of picric acid (based on the composition of the product as $C_{10}H_{10}ON_2$), and, finally, the fractional crystallization of the picrates.

All fractions which melted below 120° were combined and recrystallized from water. This gave 2.7 g. of material, m. p. 119–121°, which was identified as picric acid by mixed melting point.

All fractions melting above 155° were combined and recrystallized from water giving 5.5 g. (17%) of material; m. p. 189–191° with earlier softening. Several recrystallizations raised the melting point to 203–204°. This product was identified as 4(5)-hydroxymethylimidazole picrate (by melting point and analysis).

The fractions melting between 140 and 155° were recrystallized from water giving 6.1 g. (15%) of material; m. p. 149–151°. Further purification gave a product (m. p. 152–152.5°) which analyzed correctly for $C_{10}H_{13}O_2N_5$ or



Anal. Calcd. for $C_{10}H_{13}O_8N_5$: C, 47.66; H, 3.22. Found: C, 47.80; H, 3.25.

Identification of the latter product as *p*-4(5)-imidazolylmethylphenol picrate was accomplished as follows.

Six-tenths of a gram (0.0015 mole) of the imidazolylmethylphenol picrate was mixed with 10 ml. of water, 3 ml. of 2 *N* hydrochloric acid and extracted with 20 ml. of benzene at 60°. The aqueous layer was separated, extracted five times with 20-ml. portions of warm benzene and treated with charcoal. Removal of the water under reduced pressure gave an oil which was treated with 0.3 g. of potassium hydroxide in 5 ml. of water and placed in an ice-bath. Methylation in the usual fashion gave an oily solid (0.26 g.) (0.0013 mole) which was then dissolved in 10 ml. of water and added to a solution of 0.95 g. (0.006 mole) of potassium permanganate in 50 ml. of water. The solution was heated on the steam-bath for one hour and filtered from manganese salts giving a colorless filtrate which was concentrated to 5 ml. and acidified with 6 *N* hydrochloric acid. The resulting precipitate was recrystallized from water three times giving 0.10 g. (44%) of the product (m. p. 182–183°, cor.) which gave no depression with a known sample of *p*-methoxybenzoic acid, m. p. 183.5–184.5° (cor.) (lit., m. p. 184° cor.).

Pharmacological testing[20] has indicated that for the most part the compounds prepared thus far are relatively inactive as antihistaminic agents.

Acknowledgment is made to Dr. S. B. Binkley and Dr. L. C. Cheney of the Bristol Laboratories, Syracuse, N. Y., for their interest and encouragement.

Summary

A series of alkyl and aryl ethers of 4(5)-hydroxymethylimidazole have been prepared starting with 4(5)-chloromethylimidazole hydrochloride.

An explanation for the failure of the Williamson reaction in the aliphatic series has been offered.

N-Alkylation rather than O-alkylation occurs when 4(5)-hydroxymethylimidazole is treated with methyl iodide in the Williamson reaction.

p-4(5)-Imidazolylmethylphenol is formed when 4(5)-chloromethylimidazole hydrochloride is treated with an excess of phenol.

The ethers prepared in this study have been tested for pharmacological activity.

(20) We are indebted to Dr. H. L. Dickison of the Bristol Laboratories, Syracuse, N. Y., for this report.

SYRACUSE 10, N. Y. RECEIVED APRIL 3, 1950

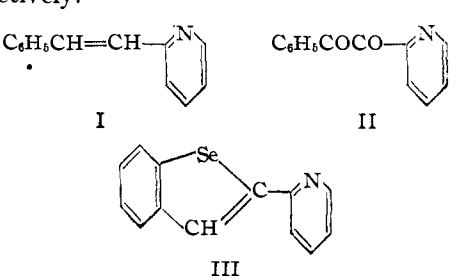
[CONTRIBUTION NO. 79 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TENNESSEE]

Reaction of α- and γ-Stilbazoles with Selenium Dioxide

BY C. A. BUEHLER, JAMES O. HARRIS AND WILLIAM F. ARENDALE

The action of selenium dioxide on alkenes leads, usually, to the formation of oxygenated substances without cleavage of the carbon chain.[1] To cite an example, stilbene gives benzil in 86% yield.[2,3]

In attempting to utilize such an oxidation for the preparation of phenyl α-pyridyl diketone (II) from α stilbazole (I) it was found that the diketone was produced together with 2-α-pyridyl selenonaphthene (III) in yields of 31 and 20%, respectively.



I II III

(1) Rabjohn, "Organic Reactions," Vol. V, John Wiley and Sons, Inc., New York, N. Y., 1949, p. 353.

(2) Astin, Moulds and Riley, *J. Chem. Soc.*, 903 (1935).

(3) Rostowsky and Lugorokin, *Ber.*, **68**, 854 (1935).