Thermal Decarboxylation of *N*-Alkoxycarbonylimidazoles. An Improved and Convenient Procedure for N-Alkylation of Imidazoles

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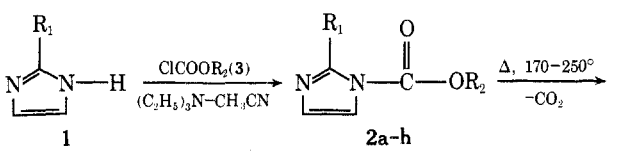
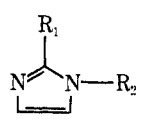
Alkylation of imidazoles at the nitrogen atom is normally achieved by reaction of imidazoles with alkyl halides or dialkyl sulfates under strongly basic conditions in organic solvents or in water. Yields are often low owing to strong water solubility of the reaction products and partial quaternization[1a,b].

In 1935 John reported that 1-carbethoxyimidazole, prepared by the reaction of imidazole with ethyl chloroformate, upon heating at 250° for 20 sec gave 1-ethylimidazole. This reaction proved to be applicable only on microscale; on scale-up large amounts of starting material remained. Reexamination of this work, however, showed that extension of the pyrolysis time solved this problem and made this reaction an attractive preparative procedure for alkylation of imidazoles.

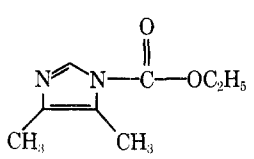
Reaction of equimolar amounts of imidazoles 1 and alkyl chloroformates 3 in the presence of 1 equiv of triethylamine in acetonitrile led to the corresponding carbamate esters **2a–h** and **5** in almost quantitative yields.



1 2a-h



4a-h



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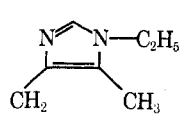

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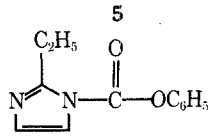

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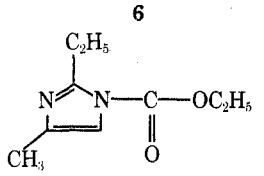

8 **a**, $R_1 = H$; $R_2 = C_2H_5$
b, $R_1 = R_2 = C_2H_5$
c, $R_1 = n\text{-}C_3H_7$; $R_2 = C_2H_5$
d, $R_1 = i\text{-}C_3H_7$; $R_2 = C_2H_5$
e, $R_1 = C_2H_5$; $R_2 = i\text{-}C_4H_9$
f, $R_1 = n\text{-}C_3H_7$; $R_2 = i\text{-}C_4H_9$
g, $R_1 = C_6H_5$; $R_2 = C_2H_5$
h, $R_1 = CH_3$; $R_2 = C_2H_5$

The crude esters were heated neat to the temperatures at which carbon dioxide evolution began and heating was prolonged for an additional 10 min. Distillation of the reaction mixtures afforded the alkylated imidazoles **4a–g** and **6** in good yields.

1-Ethyl-2-methylimidazole (**4h**) could only be obtained in 15% yield after chromatography of the tarry reaction mixture. The results are summarized in Table I.

Table I
N-Alkylated Imidazoles

Compd	Empirical formula	Yield %	Bp, °C (mm)	Decarbn temp, °C	Picrate salt[a] mp, °C
4a[b]	$C_5H_8N_2$	68	40–41(0.5)	170	170–171
4b[c]	$C_7H_{12}N_2$	65	52–53(0.01)	250	125–126
4c[d]	$C_8H_{14}N_2$	66	60–64(0.04)	200	123–124
4d	$C_8H_{14}N_2$	75	60–62(0.05	200	141–142
4e	$C_9H_{16}N_2$	59	71–72(0.1)	220	137–138
4f[d]	$C_{10}H_{18}N_2$	61	78–81(0.1)	230	129–130
4g	$C_{11}H_{12}N_2$	69	86–89(0.01)	220	173–174
4h[e]	$C_6H_{10}N_2$	15	63–67(0.02)	210	171–172
6	$C_7H_{12}N_2$	60	118–121(18)	190	170–171

[a] Satisfactory analytical data were obtained for picrate salts of all compounds listed in the table (±0.3 for C, H, and N). Ed. [b] W. John, *Ber.*, 68, 2283 (1935). [c] B. Oddo and Y. Mingoia, *Gazz. Chim. Ital.*, 58, 584 (1928); *Chem. Abstr.*, 23, 1638 (1929). [d] J. B. Rieger, *Monatsh. Chem.*, 9, 607 (1888). [e] A. Heymans, *Ber.*, 65, 320 (1932).

Attempts to synthesize N-arylated imidazoles in this manner were unsuccessful. Upon heating 1-carbophenoxy-2-ethylimidazole (7) at temperatures up to 290° no detectable carbon dioxide evolution took place and only darkening of the reaction mixture was observed.

Mechanistically this reaction might be regarded as an O → N shift and as such is comparable with the Chapman rearrangement[3] and a more recently reported rearrangement of *N*-(*p*-tolylsulfonyl)imidocarbonate.[4]

The use of this reaction in the synthesis of asymmetrically substituted imidazoles seems limited. Whereas reaction of ethyl chloroformate and 2-ethyl-4(5)-methylimidazole led to 1-carbethoxy-2-ethyl-4-methylimidazole (8) with more than 95% regioselectivity, the subsequent decarboxylation afforded a 3:1 mixture of 1,2-diethyl-4-methylimidazole and 1,2-diethyl-5-methylimidazole.

Experimental Section

General. The NMR data were obtained with a Varian T-60 spectrometer, using Me_4Si as an internal standard. The substituted imidazoles and the chloroformate esters were commercially available. A typical experiment procedure is illustrated by the synthesis of 1-ethyl-4,5-dimethylimidazole (6).

1-ethyl-4,5-dimethylimidazole (6). To a solution of 9.60 g (0.1 mol) of 4,5-dimethylimidazole and 11 g (0.11 mol) of triethylamine in 100 ml of acetonitrile was added with stirring at 10° a solution of 10.8 g (0.1 mol) of ethyl chloroformate in 20 ml of ether. After stirring at ambient temperature for 1 hr the mixture was filtered and the filtrate was taken up in 300 ml of ether. Upon washing, drying, and evaporation of the organic phase 16 g of 5 remained as a colorless oil: NMR ($CDCl_3$) 1.41 (t, 3, CH_3), 2.12 (s, 3, CH_3), 2.32 (s, 3, CH_3), 4.38 (q, 2, $-CH_2-$), 7.86 ppm (s, 1, H-2 imidazole). The crude product was heated with stirring in a round-bottom flask until a vigorous carbon dioxide evolution began (190°). After the reaction had ceased, heating was prolonged for an additional 10 min at 200°. The dark reaction mixture was distilled and afforded 7.4 g (60%) of 6 as a yellowish oil: bp 118–121° (20 mm); NMR

($CDCl_3$) δ 1.32 (t, 3, CH_3), 2.18 (s, 6, CH_3), 3.72 (q, 2, $-CH_2-$), 7.21 (s, 1, H-2 imidazole). Anal. Calcd for $C_7H_{12}N_2$: C, 67.74; H, 9.77; N, 22.50. Found: C, 67.79; H, 10.01; N, 22.38.

1-Carbethoxy-2-ethyl-4-methylimidazole (8). To a solution of 11.0 g (0.1 mol) of 2-ethyl-4(5)-methylimidazole and 11 g (0.11 mol) of triethylamine in 100 ml of acetonitrile was added dropwise with stirring at 0–5° a solution of 10.8 g (0.1 mol) of ethyl chloroformate in 30 ml of ether. After stirring for an additional 1 hr at 0° the reaction mixture was filtered. Upon washing, drying, and evaporation of the organic phase 17.3 g (95%) of **8** remained as a colorless oil: NMR ($CDCl_3$) δ 1.32 (t, 3, CH_3), 1.37 (t, 3, CH_3), 2.18 (s, 3, CH_3), 3.01 (q, 2, CH_2), 4.41 (q, 2, CH_2), 7.04 (s, 1, H-5). No traces of isomer could be detected.

On decarboxylation of **8** under the conditions used for **6** (210°), 51% of product was obtained, bp 81–85° (0.1 mm). Anal. Calcd for $C_8H_{14}N_2$: C, 69.56; H, 10.14; N, 20.28. Found: C, 69.59; H, 10.29; N, 20.12.

The NMR spectrum and TLC revealed the presence of two isomeric imidazoles in the ratio 3:1 (based on integrals). The major isomer could be identified as the normal product 1,2-diethyl-4-methylimidazole: NMR ($CDCl_3$) δ 1.38 (t, 3, CH_3), 1.41 (t, 3, CH_3), 2.25 (s, 3 CH_3), 2.64 (q, 2, CH_2), 3.87 (q, 2, CH_2), 6.58 (s, 1, H-5). The minor compound must be assigned as the isomeric 1,2-diethyl-5-methylimidazole: NMR ($CDCl_3$) δ 1.31 (t, 3, CH_3), 1.37 (t, 3, CH_3), 2.24 (s, 3, CH_3), 2.63 (q, 2, CH_2), 3.87 (q, 2, CH_2), 6.64 (s, 1, H-4).

Acknowledgment. The authors wish to thank Dr. H. M. Buck for continuous interest and encouragement.

Registry No.—**1a**, 288-32-4; **1b**, 1072-62-4; **1c**, 50995-95-4; **1d**, 36947-68-9; **1g**, 670-96-2; **1h**, 693-98-1; **2a**, 19213-72-0; **2b**, 56468-36-1; **2c**, 56468-37-2; **2d**, 56468-38-3; **2e**, 56468-39-4; **2f**, 56468-40-7; **2g**, 56468-41-8; **2h**, 56468-42-9; **3a**, 105-39-5, **3e**, 13361-35-8; **4a**, 7098-07-9; **4b**, 51807-53-5; **4c**, 56468-43-0; **4d**, 56468-44-1; **4e**, 56468-45-2; **4f**, 46056-02-4; **4g**, 56468-46-3; **4h**, 21202-52-8; **5**, 56468-47-4; **6**, 56468-48-5; **7**, 56468-49-6; **8**, 56468-50-9; 4,5-dimethylimidazole, 2302-39-8; 2-ethyl-4(5)-methylimidazole, 931-36-2; 1,2-diethyl-4-methylimidazole, 56468-51-0; 1,2-diethyl-5-methylimidazole, 56468-52-1.

Supplementary Material Available. NMR data for all compounds will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Business Office, Books and Journals Division, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.00 for photocopy or $2.50 for microfiche, referring to code number JOC-75-3279.

References and Notes

(1) (a) M. R. Grimmett, *Adv. Heterocycl. Chem.*, **12**, 103 (1970); (b) K. Hofmann, "The Chemistry of Heterocyclic Compounds", Interscience, New York, N.Y., 1953, p 175.
(2) W. John, *Ber.*, **68**, 2283 (1935).
(3) See review about the Chapman rearrangement: *Org. React.*, **14**, 1 (1965).
(4) R. F. Meyer, *J. Org. Chem.*, **28**, 2902 (1963).

Conformational Analysis of the Dibenzo[*a*,*g*]quinolizidines by Spectroscopic Methods

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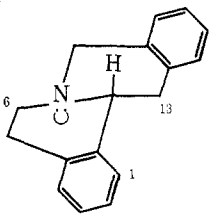
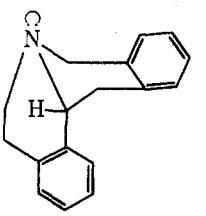
The dibenzo[*a*,*g*]quinolizidine structure forms the skeleton of the tetrahydroprotoberberine alkaloids. If rings B and C of the dibenzo[*a*,*g*]quinolizidine assume half-chair conformations, it exists in the equilibrium of one trans (**1**) and two cis conformation (**2** and **3**). The unsubstituted di-



1 **2**



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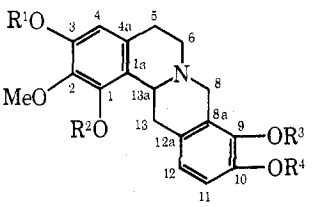
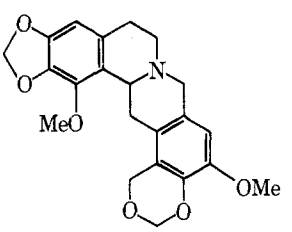


4, $R^1 = R^3 = R^4 = Me$; $R^2 = H$
5, $R^1 = R^3 = H$; $R^2 = R^4 = Me$
6, $R^1 = R^3 = Me$; $R^2 = H$; $R^4 = CO$—C₆H₄—Br
7, $R^1 = R^2 = R^3 = R^4 = Me$
8, $R^1 = R^3 = Me$; $R^2 = R^4 = H$



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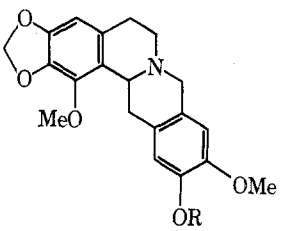
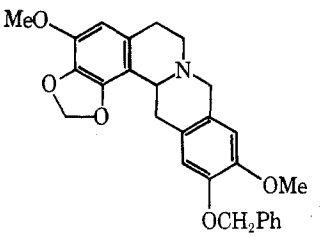


10, R = CH_2Ph
11, R = H



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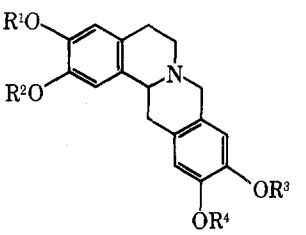
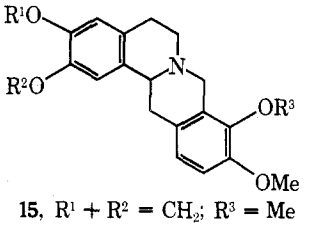
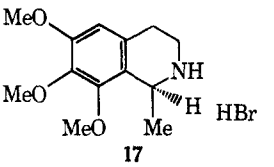


13, $R^1 = R^2 = R^3 = R^4 = Me$
14, $R^1 + R^2 = R^3 + R^4 = CH_2$



15, $R^1 + R^2 = CH_2$; $R^3 = Me$
16, $R^1 = R^2 = Me$; $R^3 = H$



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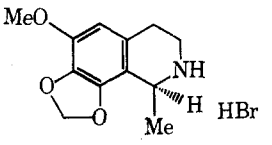

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