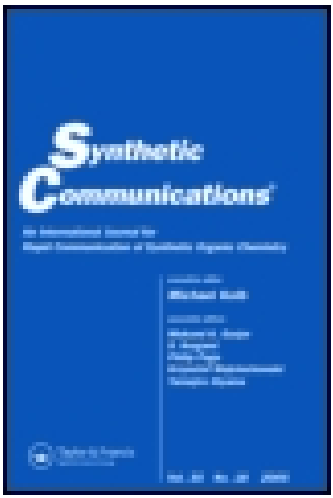
This article was downloaded by: [Michigan State University]
On: 16 February 2015, At: 07:29
Publisher: Taylor & Francis
Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

An Efficient Preparation of 7-Methoxychromanone

Zhisong Cao [a b] & Joachim G. Liehr [a]
[a] Department of Pharmacology and Toxicology , University of Texas Medical Branch at Galveston , Galveston, Texas, 77555-1031, USA
[b] The Stehlin Foundation for Cancer Research , 1918 Chenevert, Houston, TX, 77003
Published online: 21 Aug 2006.

To cite this article: Zhisong Cao & Joachim G. Liehr (1996) An Efficient Preparation of 7-Methoxychromanone, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 26:6, 1233-1245, DOI: 10.1080/00397919608003732

To link to this article: http://dx.doi.org/10.1080/00397919608003732

PLEASE SCROLL DOWN FOR ARTICLE

Taylor & Francis makes every effort to ensure the accuracy of all the information (the "Content") contained in the publications on our platform. However, Taylor & Francis, our agents, and our licensors make no representations or warranties whatsoever as to the accuracy, completeness, or suitability for any purpose of the Content. Any opinions and views expressed in this publication are the opinions and views of the authors, and are not the views of or endorsed by Taylor & Francis. The accuracy of the Content should not be relied upon and should be independently verified with primary sources of information. Taylor and

Francis shall not be liable for any losses, actions, claims, proceedings, demands, costs, expenses, damages, and other liabilities whatsoever or howsoever caused arising directly or indirectly in connection with, in relation to or arising out of the use of the Content.

This article may be used for research, teaching, and private study purposes. Any substantial or systematic reproduction, redistribution, reselling, loan, sub-licensing, systematic supply, or distribution in any form to anyone is expressly forbidden. Terms & Conditions of access and use can be found at http://www.tandfonline.com/page/terms-and-conditions

Downloaded by [Michigan State University] at 07:29 16 February 2015

SYNTHETIC COMMUNICATIONS, 26(6), 1233-1245 (1996)

AN EFFICIENT PREPARATION OF 7-METHOXYCHROMANONE

Zhisong Cao[a] and Joachim G. Liehr*

Department of Pharmacology and Toxicology, University of Texas Medical Branch at Galveston, Galveston, Texas 77555-1031, USA

Downloaded by [Michigan State University] at 07:29 16 February 2015

Abstract. The reaction of m-methoxyphenol **7** with 3-chloropropionaldehyde diethyl acetal **8** and the subsquent treatments gave the corresponding 7-methoxychromanone **6** in overall 54% yield. This method represents an efficient preparation of chromanone.

7-Methoxychromanone is a necessary precursor for the total synthesis of steroids modified to contain oxygen in their ring structures and other more complex products. Thus, studies of the preparation of this compound have received much attention since the early 1920s. A number of early reports in the literature focused on the preparation of 3-m-methoxyphenoxypropionic acid followed by cyclodehydration by using various reagents as depicted in Scheme I.

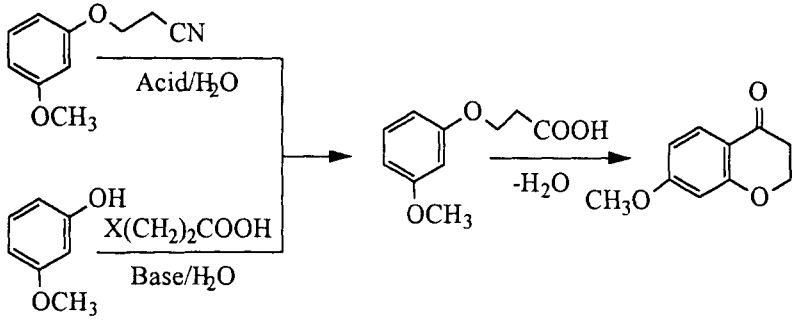
---

a. Present address: The Stehlin Foundation for Cancer Research, 1918 Chenevert, Houston, TX 77003

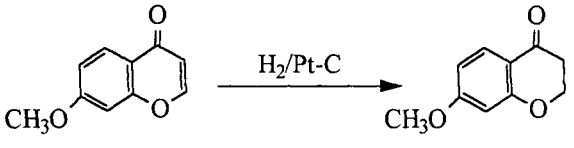
* To whom correspondence should be addressed

Copyright © 1996 by Marcel Dekker, Inc.

Scheme I



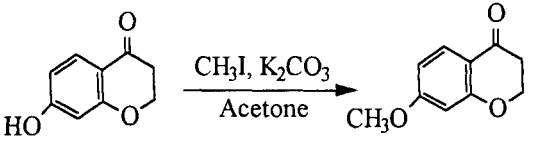
For instance, 3-m-methoxyphenoxypropionitrile when heated with concentrated hydrochloric acid[1] afforded the corresponding acid which was cyclodehydrated by phosphoric acid to form 7-methoxychromanone in very low yield. When concentrated sulfuric acid[2] was used as dehydration reagent, 7-methoxychromanone was isolated with a yield of 2%. Nucleophilic substitution reactions[2-8] between m-methoxyphenol and 3-iodo- or 3-bromopropionic acid in basic media gave 3-m-methoxyphenoxypropionic acid, which was then cyclodehydrated to 7-methoxychromanone. Overall yields in these cases varied depending on the dehydration reagents, but were generally very low. It was also reported[9] that the hydrogenation of 7-methoxychromone using a Pt-C catalyst gave the corresponding chromanone as shown in equation 1.



(1)

Downloaded by [Michigan State University] at 07:29 16 February 2015

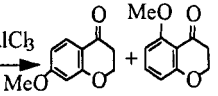
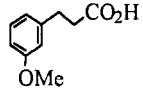
In another report[10], 7-hydroxychromanone was methylated with iodomethane to give 7-methoxy-chromanone in good yield as shown in equation 2.



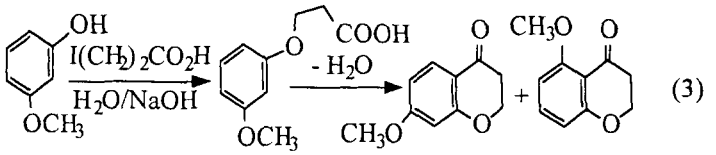
(2)

The preparation of 7-methoxychromanone was attempted by us using those reported methods. Overall yields of 7-methoxychromanone were as low as reported previously (Table 1). In addition to the expected product 7-methoxychromanone, an unexpected 5-methoxychromanone was also formed as shown in equation 3 and was isolated.

Table 1. Yields of 7-methoxychromanone by reported procedures

First step	yield	Second step	yield	Overall yield of
Reaction	A%	Reaction	5%	5%
m-$MeOC_6H_4OH$ + ICH_2CH_2COOH →	10	A $\xrightarrow{PCl_3/AlCl_3}$ 5 + 	50	5
 A		A $\xrightarrow{80\%\ H_2SO_4}$ 5	75	7.5
		A $\xrightarrow{P_2O_5 \text{ or } H_3PO_4}$ 5	65	6.5

Downloaded by [Michigan State University] at 07:29 16 February 2015



(3)

Because of the low yields, it was necessary for us to find a more efficient preparation of 7-methoxychromanone in order to realize the total synthesis of modified steroids. We thus wish to report a new preparation of this product by reaction of m-methoxyphenol **7** with 3-chloropropionaldehyde diethyl acetal **8**.

Results And Discussion

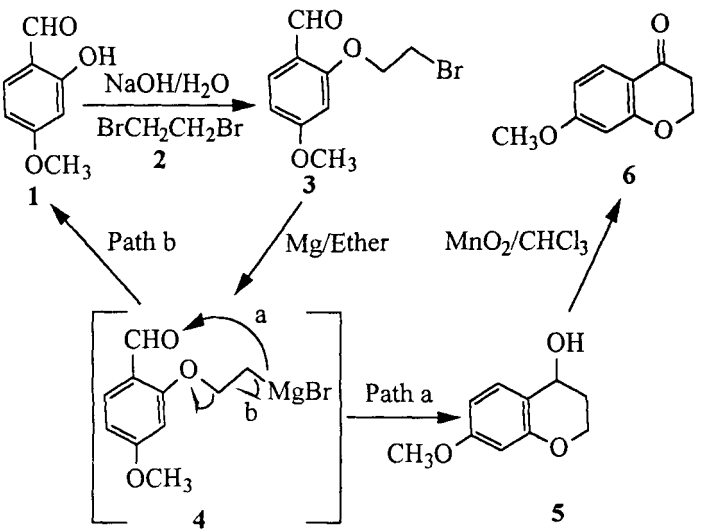
Initially, the reaction of 2-hydroxy-5-methoxybenzaldehyde **1** with 1,2-dibromoethane **2** was examined under basic conditions followed by ring-closure of the resulting ether **3** catalyzed by magnesium as depicted in Scheme II.

2-(2'-Bromo)ethoxy-5-methoxybenzaldehyde **3** was obtained as white crystals after recrystallization from diethyl ether-petroleum ether (1:1) in 90% yield, but the magnesium-catalyzed intramolecular cyclization gave only 1% of 7-methoxy-chromanone due to the dominant retro-reaction of intermediate **4** to the starting aldehyde **1** (path b, Scheme II). The overall yield by this procedure was approximately 1%.

However, the reaction of m-methoxyphenol **7** with 3-chloropropionaldehyde diethyl acetal **8** in NaOH solution under reflux for 4 h gave 3-m-methoxyphenoxy-

Downloaded by [Michigan State University] at 07:29 16 February 2015

Scheme II



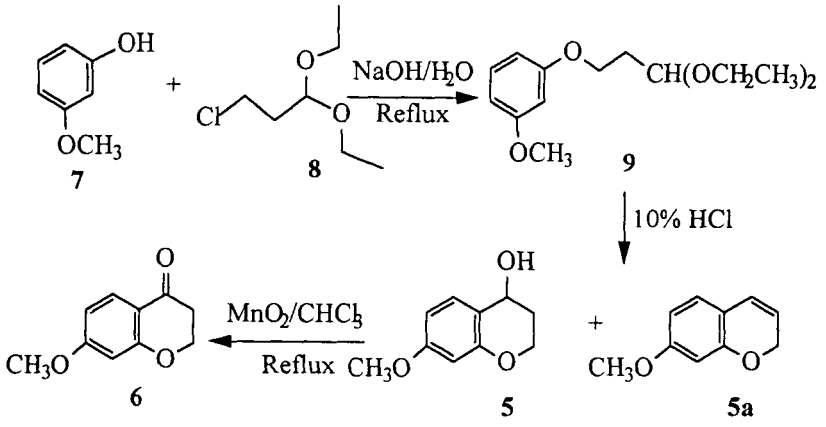
propionaldehyde diethyl acetal **9** in a yield of 91%. Treatment of the acetal **9** with aqueous 10% HCl solution under nitrogen atmosphere afforded 61% of 7-methoxychromanol **5** and 35% of 7-methoxy-3-chromene **5a**. Oxidation of the chromanol **5** by manganese dioxide gave the expected product **6** almost quantitatively as depicted in Scheme III.

The mechanism proposed for the transformation of acetal **9** to chromanol **5** and chromene **5a** is depicted in Scheme IV.

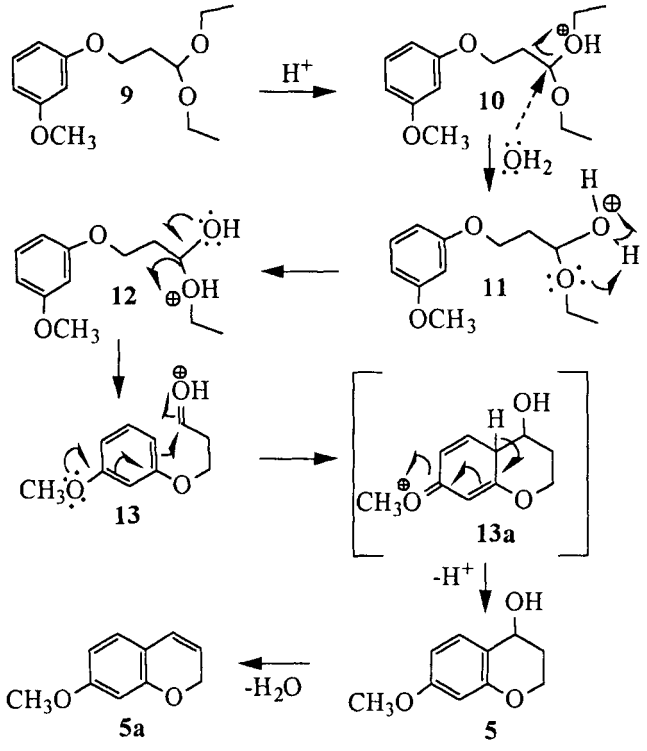
The protonation of the ethoxy group in **9** generates the intermediate **10**. The sequential replacement of a molecule of ethanol by water in **10** initially results in

Downloaded by [Michigan State University] at 07:29 16 February 2015

Scheme III



Scheme IV



Downloaded by [Michigan State University] at 07:29 16 February 2015

intermediate **11**, which after an intramolecular proton transfer reaction loses another molecule of ethanol to form the protonated aldehyde **13**. The intermediate **13** cyclizes to chromanol **5** by way of an intramolecular electrophilic aromatic substitution reaction. The further dehydration of **5** affords chromene **5a**. As a supporting factor of this mechanism, the concentration of hydrochloric acid solution plays an important role in governing the yield ratios of **5** to **5a**. Concentrated hydrochloric acid solution favors the formation of product **5a**. For example, in aqueous 15% hydrochloric acid solution, the product **5a** was isolated in a yield of 80%. In contrast, dilute hydrochloric acid solution increases the yield ratio of **5** to **5a**, but the overall transformation rate is slow. When acetal **9** was treated with 5% hydrochloric acid solution under the same reaction condition as above, the ratio of **5** to **5a** was 2 : 1. The overall transformation yield in this case was 12%.

Thus it has been shown that an efficient preparation of 7-methoxy-chromanone is realized by reactions outlined in Scheme III. The overall yield of product **6** by this new preparative pathway has been improved from 5 to 54%.

Experiment Section

General. Dry nitrogen was routinely used as the reaction atmosphere in all reactions. All glassware was baked at 80-100°C for a minimum of 2 h before being used. Melting points were obtained with an Electrothermal Melting Point apparatus and were uncorrected. All synthesized compounds were examined by ^{1}H and ^{13}C

Downloaded by [Michigan State University] at 07:29 16 February 2015

NMR and by mass spectrometry. The spectra contained only the expected peaks of the compounds reported without any indication of impurities.

The ^{1}H and ^{13}C NMR spectra of approximately 10% (w/v) solution in $CDCl_3$ were obtained at 270.05 MH_Z with a JEOL GX-270 WB NMR spectrometer. Chemical shifts are reported in parts per million (δ scale), employing tetramethylsilane as an internal standard. In reporting the NMR data, we have used the following abbreviations: coupling constants in Hertz (J), singlet (s), doublet (d), triplet (t), and multiplet (m).

Mass Spectra were recorded using a Nermag model R 10 - 10 C mass spectrometer with a resolution of 3300-5000.

Solvents routinely used such as tetrahydrofuran, diethyl ether, and methylene chloride were dried and distilled from CaH_2. Silica gel (230-400 mesh, Aldrich) for column chromatography was used for all product separations. Eastman chromagram (Silica gel with fluorescent indicator on polyethylene) sheets were employed in thin-layer chromatography (TLC) separations.

Preparation of 2-(2'-bromo)ethoxy-5-methoxybenzaldehyde 3. o-Hydroxy-p-methoxybenzaldehyde (5.0 g, 0.033 moles) was added to a stirred solution of NaOH (2.0 g) in 30 ml of distilled and deionized water After stirring this mixture at room temperature for 10 min, a homogeneous solution was obtained, to which was

Downloaded by [Michigan State University] at 07:29 16 February 2015

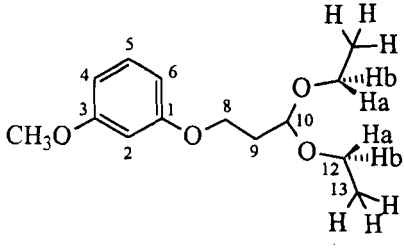
Downloaded by [Michigan State University] at 07:29 16 February 2015

added 1 ml (2.18 g, 0.012 moles) of 1,2-dibromoethane. The mixture was refluxed for 15 h. After cooling to room temperature, a milk-like suspension was obtained, which was neutralized with acetic acid and extracted with 300 ml of methylene chloride (3 X 100 ml). The combined organic extracts were dried over K_2CO_3 for 5 h. After solvents were removed by rotary evaporator, the residue was chromatographically separated with diethyl ether-petroleum ether (1 : 2) as eluent. Pure **3** (2.7 g, 91%) was obtained as white crystalline product, which gave one spot by TLC with diethyl ether-petroleum ether solvent system. An analytically pure sample (recrystallized from diethyl ether) had a mp 124°C. ^{1}H NMR: 3.70 (2H, t, 2-$OCH_2C\underline{H}_2Br$, J = 6.2 Hz), 3.87 (3H, s, 4-$OC\underline{H}_3$), 4.38 (2H, t, 2-$OC\underline{H}_2CH_2Br$, J = 6.0 Hz), 6.42 (1H, s, 3-Ar$\underline{H}$), 6.59 (1H, d, 5-Ar$\underline{H}$, J = 8.8 Hz), 7.84 (1H, d, 6-Ar$\underline{H}$, J = 8.4 Hz). The mass spectrum showed a M^+ peak at m/z 259.

Cyclization of compound 3 to 7-methoxychromanol 5 catalyzed by Mg. A few crystals of iodine and 0.4 g (0.016) of magnesium chips were added to a stirred solution of 2.0 g (0.008 moles) of compound **3** in 50 ml of dry tetrahydrofuran (freshly distilled from CaH_2) under N_2. The mixture was refluxed under nitrogen atmosphere for 4 h while stirring. After cooling to room temperature, the reaction mixture was poured into 200 ml of ice-water with stirring and was then neutralized with acetic acid. The obtained neutral solution was extracted with 200 ml of diethyl ether (4 X 50 ml). The combined extracts were dried over anhydrous sodium sulfate for 4 h. After evaporation of solvents, the residue was chromatographically separated with diethyl ether-petroleum ether as eluent. The pure product **5** (20 mg, 1%) was

obtained as a viscous liquid and gave one spot by TLC with diethyl ether-petroleum ether (R_f = 5.5). ^{1}H NMR: 1.96 (2H, m, C3-H_2), 2.47 (1H, s, C4-OH), 2.73 (3H, s, C7-OCH_3), 4.18 (2H, m, C2-H_2), 4.65 (1H, m, C4-H), 6.35 (1H, s, C8-H), 6.48 (1H, d, C6-H, J = 8.4 Hz), 7.14 (1H, d, C5-H, J = 8.4 Hz); ^{13}C NMR: 30.86 (C3), 55.14 (C7-OCH_3), 61.84 (C2), 62.59 (C4), 101.18 (C8), 107.68 (C6), 116.84 (C4a), 130.51 (C5), 155.50(C7), 160.61 (C8a). The mass spectrum showed a M^+ peak at m/z 180.

Preparation of 3-m-methoxyphenoxypropionaldehyde diethyl acetal 9. Forty g (0.323 moles) of m-methoxyphenol was added to a stirred solution containing 18 g (0.450 moles) of sodium hydroxide in 50 ml of distilled and deionized water. The resulting solution was stirred at room temperature for 30 min. To the above solution was added 30 ml (0.172 moles) of 3-chloro-propionaldehyde diethyl acetal (95% pure, d = 0,995, Aldrich, Milwaukee, WI). The mixture was refluxed for 15 h. After cooling to room temperature, the solution was neutralized with acetic acid and then extracted with 300 ml of diethyl ether (3 X 100 ml). The combined organic extracts were dried over anhydrous sodium sulfate for 4 h. After evaporation of solvents, fractional distillation afforded 39.7 g (91%) of **9** as a colorless liquid. TLC showed one spot (Rf = 5.0). ^{1}H NMR (numbering system is shown as right below): 1.18 (6H, t, C13H_3, J = 7.0 Hz), 2.05 (2H, m, C9H_2), 3.50 (2H, m, C12HaHb), 3.64 (2H, m, C12HaHb), 3.71 (3H, s, 3-CH_3), 3.99 (2H, t, C8H_2, J = 6.2 Hz), 4.72 (1H, t, C10H,



Downloaded by [Michigan State University] at 07:29 16 February 2015

J = 6.2 Hz), 6.45 (3H, m, C2H, C4H, C6H), 7.12 (1H, t, C5H); ^{13}C NMR: 15.07 (C13), 33.84 (C9), 54.87 (3-O$\underline{C}H_3$), 61.54 (C8), 64.07 (C12), 100.33 (C10), 101.16 (C2), 106.20 (C4), 106.79 (C6), 129.55 (C5), 160.18 (C3), 160.81 (C6). The mass spectrum showed a M^+ peak at m/z 254.

Downloaded by [Michigan State University] at 07:29 16 February 2015

Cyclization of compound 9 to 7-methoxychromanol 5 and 7-methoxychromene 5a catalyzed by hydrochloric acid. To a stirred solution containing 28 g (0.110 moles) of **9** in 200 ml of tetrahydrofuran immersed in an ice bath was slowly added 150 ml of aqueous 10% hydrochloric acid under nitrogen atmosphere. The solution was stirred at 0^{0}C for 1 h. After warming to room temperature, the solution was stirred for another 4 h. The resulting solution was neutralized with sodium bicarbonate and was then extracted with 400 ml of diethyl ether (4 X 50 ml). The combined organic extracts were dried over anhydrous sodium sulfate for 4 h. After evaporation of solvents, the residue was chromatographically separated with diethyl ether-petroleum ether as eluent, which afforded 12 g (61%) of **5** and 6 g (35%) of **5a** as a colorless liquid. The ^{1}H NMR data and TLC Rf value for **5** prepared by this procedure were the same as those reported above. ^{1}H NMR for **5a**: 5.62 (2H, s, C2H_2), 6.47 (1H, d, C3H, J = 8.5 Hz), 7.21 (3H, m, C4H, C6H, C8H), 7.70 (1H, d, C5H, J = 8.1 Hz); ^{13}C NMR for **5a**: 55.29 (C7-O$\underline{C}H_3$), 65.59 (C2), 101.75 (C3), 106.93 (C4), 115.67 (C4a), 118.80 (C8), 124.21 (C6), 127.19 (C5), 155.32 (C7),160.59 (C8a). The mass spectrum showed a M^+ peak at m/z 162.

Oxidation of 7-methoxychromanol 5 to 7-methoxychromanone 6. A

solution containing 11 g (0.611 moles) of chromanol **5** and 100 g of activated manganese dioxide[11] in 250 ml of chloroform was refluxed for 15 h. The mixture was filtered while warm, the precipitate was thoroughly washed with chloroform, and the combined washes were concentrated. Filtration of the concentrate through 300 g of silica gel using diethyl ether-petroleum ether as eluent afforded 10.7 g (98%) of 7-methoxychromanone **6**. TLC with diethyl ether-petroleum ether showed one spot. Melting point and ^{1}H NMR data were identical to those reported in the literature[1-8].

Acknowledgement. The authors wish to thank Mr. Edward Ezell for NMR data and Dr. Khingkan Lertratananghoon for mass data. Financial support from the NIH, NCI (grant CA 43232) is gratefully acknowledged.

Supplementary material available. Copies of ^{1}H NMR and ^{13}C NMR spectra of compounds **3**, **5**, **5a**, and **9** (9 pages).

References

1. Loudon, J. D. and Razdan, R. K., J. Chem. Soc., 1954, 4299.
2. Bachmann, G. B. and Levine, H. A., J. Amer. Chem. Soc., 1948, 70, 599.
3. Chen, Tsien-Chien; Sun, Chang-Sheng; Soong, Hong-Tsiang; and Chang, Chi-Chek, Hua Hsueh Hsueh Pao, 1956, 22, 455.
4. Perkin, W. H.,Jr; Ray, J. N.; and Robinson, R. J., Chem. Soc., 1927, 2094.
5. Chichibabin, A. E., Ber., 1924, 57A, 617.
6. Pfeiffer, P.; and Oberlin, J., Ber., 1924, 57B, 208-43.
7. Chichibabin, A. E.; and Nikitin, I. V., J. Russ. phys. Chem. 43, 1185.

Downloaded by [Michigan State University] at 07:29 16 February 2015

8. Perkin, W. H., Jr; and Robinson, R., Proc. Chem. Soc.., 28, 7-8.

9. Pfeiffer, P.; and Grimmer, J., Ber. 1917, 50, 911-927.

10. Dann, O.; and Hofmann, H., Naturwissenschaften, 1961, 48, 162.

11. Henbest, H. B.; Jones, E. R. H.; and Owen, T. C., J. Chem. Soc., 1957, 4909.

(Received in the USA 09 September 1995)

Downloaded by [Michigan State University] at 07:29 16 February 2015

Downloaded by [Michigan State University] at 07:29 16 February 2015