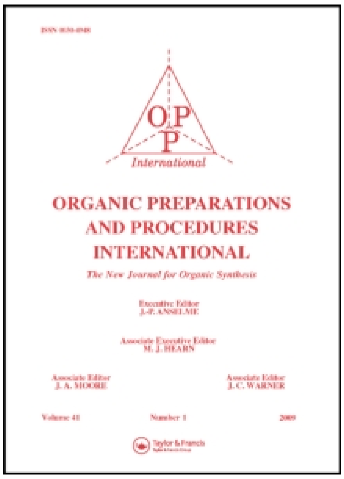
This article was downloaded by:
On: *27 January 2011*
Access details: *Access Details: Free Access*
Publisher *Taylor & Francis*
Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Organic Preparations and Procedures International

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

TWO EFFICIENT SYNTHESES OF INDOLE-3-PROPIONIC ESTERS AND ACIDS. FURTHER APPLICATIONS OF MELDRUM'S ACID

Diane S. Farlow[a]; Michael E. Flaugh[a]; Sharon D. Horvath[a]; Edward R. Lavagnino[a]; Paul Pranc[a]
[a] The Lilly Research Laboratories Eli Lilly and Company, Indianapolis, Indiana

To cite this Article Farlow, Diane S. , Flaugh, Michael E. , Horvath, Sharon D. , Lavagnino, Edward R. and Pranc, Paul(1981) 'TWO EFFICIENT SYNTHESES OF INDOLE-3-PROPIONIC ESTERS AND ACIDS. FURTHER APPLICATIONS OF MELDRUM'S ACID', Organic Preparations and Procedures International, 13: 1, 39 — 48

To link to this Article: DOI: 10.1080/00304948109356499

URL: http://dx.doi.org/10.1080/00304948109356499

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: http://www.informaworld.com/terms-and-conditions-of-access.pdf

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

ORGANIC PREPARATIONS AND PROCEDURES INT. 13(1), 39-48 (1981)

Downloaded At: 12:13 27 January 2011

TWO EFFICIENT SYNTHESES OF INDOLE-3-PROPIONIC ESTERS AND ACIDS. FURTHER APPLICATIONS OF MELDRUM'S ACID

Diane S. Farlow, Michael E. Flaugh*, Sharon D. Horvath,
Edward R. Lavagnino* and Paul Pranc

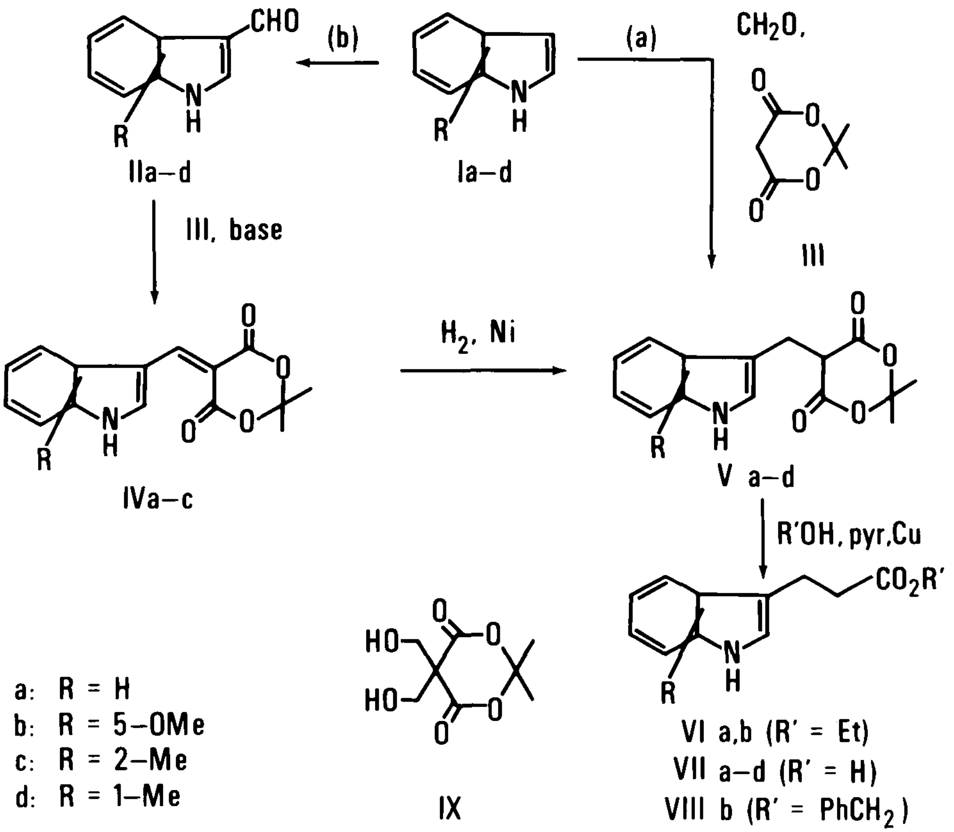
The Lilly Research Laboratories
Eli Lilly and Company
Indianapolis, Indiana 46285

The currently accepted methods of choice for the synthesis of indole-3-propionic acid and its esters are laborious and costly.[1] It has been claimed that indoles can be condensed directly with acrylic acid or its derivatives,[2] but this method has failed to give satisfactory results in our hands. Recently a synthesis of β-substituted indole-3-propionic esters utilizing aldehydes, indole, and Meldrum's acid was reported by Oikawa et al.[3] Unfortunately, this method cannot be used to make simple indole-3-propionic esters unless significantly modified. This report offers such a modification as well as an alternative method that allows one to synthesize an even wider variety of substituted indole-3-propionic acids and acids.

We have found that Meldrum's acid (III) and formaldehyde condense very efficiently with indoles when the molar ratio of these three reactants is 1:1:1 (Scheme I, path a). The ratio of 1:2:1 stressed by Oikawa et al. fails in the case of formaldehyde, possibly because the excess formaldehyde leads to the

© 1981 by Organic Preparations and Procedures Inc.

rapid formation of the bis-hydroxymethyl adduct IX. Decarboxylative ethanolysis of the lactone V under the conditions described by Oikawa *et al.* proceeds smoothly; however, the



a: R = H
b: R = 5–OMe
c: R = 2–Me
d: R = 1–Me

presence of copper salts remaining in the product mixture, even after filtration, gives rise to a severe air sensitivity that can result in disastrous yields unless dealt with promptly. Thus one must either distill the product from the reaction mixture forthwith or else immediately wash out the copper salts with ammonium chloride solution. We prefer the latter expedient. After the ammonium chloride washing, the product can be isolated without difficulty. Use of benzyl

Downloaded At: 12:13 27 January 2011

alcohol or water in the decarboxylative solvolysis produces good yields of the benzyl ester or carboxylic acid, respectively. The results from several examples are listed in Table 1.

TABLE 1. Yields from Condensations and Solvolysis

	Condensation		Solvolysis	
Indole	Yield of V (Path a)	Yield of V* (Path b)	Solvent	Yield of Esters or Acid
Ia	87%	86%	EtOH/pyr H_2O/pyr	61% (VIa) 90% (VIIa)
Ib	84%	89%	EtOH/pyr BzOH/pyr H_2O/pyr	83% (VIb) 67% (VIIIb) 80% (VIIb)
Ic	0	69%	H_2O/pyr	91% (VIIc)
Id	73%	-	H_2O/pyr	77% (VIId)

*Overall yield based on corresponding aldehyde II.

An alternate route to the intermediate V involves condensation of III with indole-3-carboxaldehydes followed by hydrogenation (Scheme I, path b). This alternative is worthy of mention because a number of these aldehydes are commercially available or they can be easily synthesized. The condensation and hydrogenation steps are particularly convenient and give an overall yield that is comparable to that obtained by path a (see Table 1). Furthermore, this second route has a much broader scope. An example is the case of 2-methylindole (Ic), which does not appear to undergo the Mannich-type condensation but is amenable to the alternate route.

Downloaded At: 12:13 27 January 2011

EXPERIMENTAL

The indoles I and II were commercially available. Meldrum's acid III is also commercially available but for this study we prepared large quantities from malonic acid and isopropenyl acetate.[4] Melting points are uncorrected. NMR spectra were determined at 60 MHz on a Varian Associates T-60 Spectrometer. Mass spectra were determined on a CEC 21-110 spectrometer at an ionizing voltage of 70 eV. Infrared spectra were obtained using a Perkin-Elmer Model 457 diffraction grating spectrophotometer.

Downloaded At: 12:13 27 January 2011

5-(Indol-3-ylmethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (IVa).- A solution of 25 g (0.17M) of indole-3-carboxaldehyde in 500 ml of hot ethyl alcohol was treated with 2 ml of piperidine followed by the addition of 25 g (0.17 ml of Meldrum's acid (III). III rapidly dissolved in the warm solution which turned yellow and after a few minutes crystals began to form. After heating for another 0.17 h the reaction mixture was allowed to cool slowly and was then refrigerated. The crystals were collected, washed with cold ethyl alcohol, and dried to provide 41 g (88%) of IVa, mp 237-238°. IR (mull): 3160, 1730, 1680, 1545, 1380 cm^{-1}; ^1H NMR (DMSO): δ 1.7 (s, 6H, $2CH_3$), 7.2-8.1 (m, 4H, Ar), 8.8 (s, 1H, -C$\underline{H}$=C), 9.4 (s, 1H, N-C$\underline{H}$=C), 13.0 (bs, 1H, NH); MS: m/e 271 (M^+).

Anal. Calcd for $C_{15}H_{13}NO_4$: C, 66.41; H, 4.83; N, 5.16

Found: C, 66.23; H, 4.96; N, 5.08

5-(5-Methoxyindol-3-ylmethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (IVb).- Using the same procedure as above, IVb, mp 246° (dec.), was prepared in 93% yield from 5-methoxyindole-3-carboxaldehyde. IR (KBr): 3170, 1730, 1675, 1535, 1480, 1360, 1270, 1190 cm^{-1}; ^1H NMR (DMSO): δ 1.7 (s, 6H, $2CH_3$), 3.9 (s, 3H, OCH_3), 6.8-7.8 (m, 3H, Ar), 8.8 (s, 1H, C$\underline{H}$=C), 9.3 (s, 1H, N-C$\underline{H}$=C), 12.8 (bs, 1H, NH).

Downloaded At: 12:13 27 January 2011

Anal. Calcd for $C_{16}H_{15}NO_5$: C, 63.78; H, 5.02; N, 4.65
Found: C, 64.03; H, 5.09; N, 4.91

5-(2-Methylindol-3-ylmethylidene)-2,2-dimethyl-1,3-dioxane-4,6-dione (IVc).- Using 2-methylindole-3-carboxaldehyde as starting material, IVc was similarly prepared in 73% yield, mp 228-230° (dec). IR (mull): 3140, 1720, 1685, 1550, 1360, 1275 cm^{-1}; ^1H NMR (DMSO): δ 1.8 [s, 6H, $-C-(CH_3)_2$], 2.6 (s, 3H, CH_3), 7.1-7.6 (m, 4H, Ar), 8.7 (s, 1H, $-C\underline{H}=C$), 12.6 (bs, 1H, NH); MS: m/e 285 (M^+).

Anal. Calcd for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91
Found: C, 67.52; H, 5.57; N, 4.82

5-(Indol-3-ylmethyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (Va).- A solution of 25 g (0.17M) of III, 20 g (0.17M) of indole and 13.8 ml (0.17M) of a 37% solution of formaldehyde along with 1.0 g of proline (catalyst, see Ref. 3) in 100 ml of acetonitrile was stirred for 16 hrs at room temperature and then concentrated to a brown foam. The product was crystallized by dissolving in 100 ml of warm methyl alcohol and adding 500-600 ml of H_2O. After cooling, the tan crystals that separated were collected and dried providing 40 g (87%) of Va, mp 106-108°. IR (mull): 3420, 1790, 1750, 1380, 1300, 1210 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.4/1.7 (2s, 6H, $2CH_3$), 3.7 (m, 3H, $-CH_2-CH-$), 7.1-7.4 (m, 4H, Ar), 7.8 (m, 1H, $N-C\underline{H}=C$), 8.3 (bs, 1H, NH).

Anal. Calcd for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.14
Found: C, 65.80; H, 5.47; N, 5.08

Va from IVa.- A solution of 30 g (0.11M) of IVa in 770 ml of THF was hydrogenated at room temperature in the presence of 3 g of Raney nickel at an initial hydrogen pressure of 60 psi.

The theoretical hydrogen uptake was achieved after 3 hrs. Removal of the catalyst by filtration, concentration of the filtrate and recrystallization of the residue from THF-hexane provided 28.9 g (98%) of Va, mp 105-107°. The product was identical in all respects with Va obtained from the reaction of indole, formaldehyde, and Meldrum's acid.

<u>5-(5-Methoxyindolyl-3-ylmethyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (Vb)</u>.- This compound was prepared by path a starting with 5-methoxyindole. The brown foam obtained was recrystallized from warm acetone:H_2O (1:1) to yield 8.7 g (84%) of Vb, mp 135-136°. IR (mull): 3420, 1780, 1740, 1360, 1290, 1200 cm^{-1}; ^1H NMR (DMSO): δ 1.5/1.7 [2s, 6H, $-C-(CH_3)_2$], 3.2 (bd, 2H, $-C\underline{H}_2-CH$), 3.8 (s, 3H, CH_3O), 4.7 (t, 1H, $-CH_2-C\underline{H}-$), 6.6-7.4 (m, 4H, Ar+N-C$\underline{H}$=C), 11.4 (bs, 1H, NH).

<u>Anal</u>. Calcd for $C_{16}H_{17}NO_4$: C, 63.36; H, 5.56; N, 4.62
Found: C, 63.66; H, 5.43; N, 4.92

<u>Vb from IVb</u>.- Hydrogenation of IVb using the conditions for preparing Va gave a 96% yield of Vb identical with the material obtained from the reaction of 5-methoxyindole, formaldehyde, and Meldrum's acid.

<u>5-(2-Methylindol-3-ylmethyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (Vc)</u>.- This compound was prepared from IVc by hydrogenation using the same conditions as for preparing Va. The yield of Vc, mp 115-117°, was 94%. IR ($CHCl_3$): 3470, 3000, 1790, 1750, 1470, 1435, 1340, 1310, 1285 cm^{-1}; ^1H NMR (DMSO): δ 1.4/1.7 [2s, 6H, $-C(CH_3)_2$], 2.3 (s, 3H, $-CH_3$), 3.4 (d, 2H, $-CH_2-$), 4.3 (t, 1H, -CH; exchanges with D_2O), 6.8-7.5 (m, 4H, Ar), 10.7 (bs, 1H, NH).

Downloaded At: 12:13 27 January 2011

Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.87; H, 5.96; N, 4.88
Found: C, 67.16; H, 5.93; N, 5.08

5-(1-Methylindol-3-ylmethyl)-2,2-dimethyl-1,3-dioxane-4-6-dione (Vd).- Starting with N-methyl indole, Vd was prepared by the procedure used for preparing Va by path a. The crude reaction product was recrystallized from methyl alcohol providing a 73% yield of Vd; yellow crystals, mp 127-130°. IR ($CHCl_3$): 3020, 1790, 1750, 1400, 1340, 1290, 1250 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.4/1.6 [2s, 6H, $-C(CH_3)_2$], 3.2-3.8 (m, 6H, $N\text{-}C\underline{H}_3+C\underline{H}_2\text{-}C\underline{H}$), 6.8-7.9 (m, 5H, Ar+$N\text{-}C\underline{H}{=}C$).

Anal. Calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.88
Found: C, 67.09; H, 6.32; N, 4.70

Indole-3-Propionic Acid (VIIa).- A mixture of 19 g (0.069M) of Va, 0.5 g of powdered copper, 180 ml of pyridine and 20 ml of water was refluxed for 3 hrs under a nitrogen atmosphere. The reaction mixture was cooled, filtered and the filtrate concentrated to an oily residue. This was taken up in 1 L. of diethyl ether and washed successively with 500 ml of 1N HCl, 500 ml of 20% NH_4Cl, and 500 ml of H_2O. After drying over Na_2SO_4 the solvent was removed under reduced pressure and the residue recrystallized from ether-hexane to provide 11.8 g (90%) of VIIa, mp 123-125°C, lit[2a] 124-126°. IR ($CHCl_3$): 3480, 3000, 2900, 1710, 1450, 1410 cm^{-1}; ^1H NMR (DMSO): δ 2.3-3.6 (m, 4H, $-CH_2\text{-}CH_2-$), 6.8-7.7 (m, 5H, Ar+$N\text{-}C\underline{H}{=}C$), 10.9 (bs, 1H, exchanges with D_2O), 10.9 (very broad singlet, 1H, exchanges with D_2O); MS: m/e 189 (M^+).

Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.83; H, 5.86; N, 7.40
Found: C, 70.09; H, 5.74; N, 7.67

Downloaded At: 12:13 27 January 2011

5-Methoxyindole-3-propionic acid (VIIb).- By a procedure similar to that for the preparation of VIIa, VIIb was prepared from Vb in 80% yield, mp 133-135° (recrystallized from chloroform-hexane), lit.[5] 136°. IR (mull): 3420, 3340, 1690, 1585, 1485, 1275, 1220, 1210, 1180, 1030 cm^{-1}; ^{1}H NMR (DMSO): δ 2.4-3.2 (m, 4H, $-CH_2-CH_2-$), 3.8 (s, 3H, $-OCH_3$), 6.6-7.4 (m, 4H, Ar+-N-C$\underline{H}$=C), 10.7 (bs, 1H, exchanges with D_2O).

Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39
Found: C, 65.54; H, 5.93; N, 6.33

2-Methylindole-3-propionic acid (VIIc).- In a manner similar to the preparation of VIIa and VIIb, VIIc was prepared in 91% yield, mp 125-217° (recrystallized from CH_2Cl_2-hexanes), lit.[6] 138°. IR ($CHCl_3$): 3480, 3010, 2920, 1715, 1470, 1300 cm^{-1}; ^{1}H NMR (DMSO): δ 2.2-3.5 (m, 4H, $-CH_2-CH_2-$), 2.4 (s, 3H, $-CH_3$), 6.8-7.6 (m, 4H, Ar), 10.7 (bs, 1H, exchanges with D_2O), 11.9 (bs, 1H, exchanges with D_2O).

Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89
Found: C, 71.21; H, 6.15; N, 7.04

N-Methylindole-3-propionic acid (VIId).- The procedure used for preparing VIId was the same as for the preparation of VIIa except that the crude product obtained was dissolved in CH_2Cl_2 before washing successively with 1N HCl, 20% NH_4Cl and H_2O. A 77% yield of VIId was obtained, mp 119-121°, lit[7] 123-125°. IR (mull): 1700, 1320, 1280, 1145, 1000, 920, 810, 720 cm^{-1}; ^{1}H NMR (DMSO): δ 2.3-3.2 (m, 4H, $-CH_2-CH_2-$), 3.7 (s, 3H, NCH_3), 6.8-7.7 (m, 5H, Ar+N-C$\underline{H}$=C), 12.1 (bs, 1H, exchanges with D_2O, $-CO_2H$).

Downloaded At: 12:13 27 January 2011

Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.44; N, 6.91
Found: C, 71.05; H, 6.73; N, 6.80

Ethyl Indole-3-propionate (VIa).- To a solution of 60.0 g (0.22M) of Va in 2 L. of 9:1 pyridine absolute ethyl alcohol was added 2.0 g of copper powder, and the mixture was refluxed under nitrogen for 16 hrs. After cooling and filtering, the solvents were removed under reduced pressure. The residual oil that remained taken up in ether and washed successively with 1N HCl, 20% NH_4Cl and H_2O. The ether solution was dried over Na_2SO_4 and concentrated to a residue that yielded 29 g (61%) of VIa after recrystallization from ethyl ether-hexanes, mp 36-38°, lit.[8] 43-45°. IR (mull): 3350, 1730, 1290, 1240, 1205 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.2 (t, 3H, $-CH_3$), 2.5-3.3 (m, 4H, $-CH_2-CH_2$), 4.2 (q, 2H, $-O-CH_2-$), 6.8-8.4 (m, 6H, Ar+NH+ -CH=); MS: m/e 217 (M^+).

Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45
Found: C, 71.64; H, 7.21; N, 6.25

Ethyl 5-Methoxyindole-3-propionate (VIb).- Using the procedure described for the preparation of VIa except that the reaction mixture was refluxed only 3 hrs, Vb was converted to VIb in 83% yield, mp 72-3° (recrystallized from toluene-hexane). IR ($CHCl_3$): 3490, 3005, 1720, 1625, 1585, 1485, 1455, 1380, 1290, 1175, 1060 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.2 (t, 3H, $-CH_3$), 2.5-3.3 (m, 4H, $-CH_2-CH_2-$), 3.8 (s, 3H, $-OCH_3$), 4.1 (q, 2H, $-OCH_2C\underline{H}_3$), 6.7-8.2 (m, 5H, Ar+N$\underline{H}$-C$\underline{H}$=).

Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66
Found: C, 68.30; H, 6.83; N, 5.45

Downloaded At: 12:13 27 January 2011

Benzyl 5-Methoxyindole-3-propionate (VIIIb).- A similar procedure to that given for the preparation of VIb except using benzyl alcohol in place of the ethyl alcohol provided VIIIb in 67% yield, mp 102-103°. IR ($CHCl_3$): 3495, 3020, 1730, 1625, 1590, 1485, 1455, 1290, 1175 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.5-3.3 (m, 4H, $-C\underline{H}_2-C\underline{H}_2-$), 3.8 (s, 3H, $-OCH_3$), 5.1 (s, 2H, $-OC\underline{H}_2$), 6.6-7.5 (m, 4H, Ar+N-C$\underline{H}$=C), 7.3 (s, 5H, $-CH_2-Ar$), 7.9 (bs, 1H, NH).

Anal. Calcd for $C_{19}H_{19}NO_3$: C, 73.77; H, 6.19; N, 4.53
Found: C, 73.52; H, 6.13; N, 4.53

Downloaded At: 12:13 27 January 2011

REFERENCES

1. (a) Y. G. Perron and W. F. Minor, J. Org. Chem., 24, 1165 (1959).
   (b) L. D. Basanagoudar and S. Siddappa, J. Karnatak. Univ., 17, 33 (1972); C.A. 82, 111898m (1975).
2. (a) H. E. Johnson and D. G. Crosby, J. Org. Chem., 25, 569 (1960).
   (b) H. E. Johnson and D. G. Crosby, ibid., 28, 2030 (1963).
3. Y. Oikawa, H. Hirasawa, and O. Honemitsu, Tetrahedron Lett., 1759 (1978).
4. D. Davidson and S. A. Berhard, J. Am. Chem. Soc., 70, 3426 (1948).
5. H. S. B. Barrett, W. H. Perkin, and R. Robinson, J. Chem. Soc., 2942 (1929).
6. J. Harley-Mason, ibid., 2433 (1952).
7. H. R. Snyder and E. L. Eliel, J. Am. Chem. Soc., 71, 663 (1949).
8. L. I. Smith and A. W. Sogn, ibid., 67, 822 (1945).

(Received January 21, 1980; in revised form May 10, 1980)