[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF MICHIGAN]

Synthesis of Potential Anticancer Agents. VI. N-(3-Hydroxypropyl)benzaldimine and Related Compounds^{1,2}

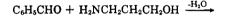
WYMAN R. VAUGHAN AND ROBERT S. KLONOWSKI³

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The condensation product of benzaldehyde with 3-aminopropanol is identified as the Schiff base rather than 2-phenyltetrahydro-1,3-oxazine as previously reported. Its behavior with acid chlorides is described, and its use as an intermediate in the preparation of 3-N-benzylaminopropyl tosylate is considered. This substance was desired as an intermediate in the synthesis of N-benzylazetidine, for which two other potential routes involving 3-aminopropanol derivatives are described.

In connection with studies directed toward the preparation of N-benzylazetidine,² it was desired to develop a satisfactory method for preparing 3-benzylaminopropyl 4-toluenesulfonate for cyclization to the desired azetidine. The reductive alkylation of 3-aminopropanol with benzaldehyde and tosylation of the product proved unsatisfactory since the tosylation reaction afforded a difficultly separable mixture of hydrochlorides of the desired ester and pyridine. Isolation by neutralization was not feasible since the ester cyclizes to N-benzylazetidine, a reaction best carried out as a discrete step³ to avoid serious competition from polymerization. The present paper describes our experience with other routes which were explored.

Since the Schiff base from benzaldehyde and 3aminopropanol, N-(3-hydroxypropyl)benzaldimine (I), is readily accessible and in principle should be readily esterified, the condensation was carried out in benzene by azeotropic distillation of the water produced (Chart I). Such a condensation had been reported earlier to yield 2-phenyl-1,3-



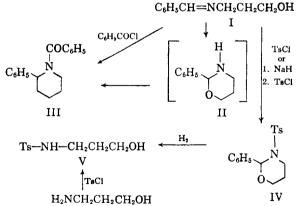


Chart I. Preparation and reactions of N-(3-hydroxypropyl)benzaldimine

tetrahydrooxazine (II) on the grounds that the product afforded a benzovl derivative which did not undergo the facile hydrolysis expected of an ester.⁴ The derivative (III) thus was assigned the structure of II-N-benzamide. We obtained the same condensation product as reported earlier,⁴ but though it reacted as reported with benzovl chloride⁴ to give III, an examination of the infrared and ultraviolet absorption spectra support structure I as against structure II: thus there is a band at 1650 cm.⁻¹, characteristic of Schiff bases; and there is an absorption maximum at 246.7 $m\mu$ (ϵ 15,400) also characteristic of Schiff bases^{5a} of the benzaldimine type. The benzoyl derivative, III, shows no absorption in the region 220-260 $m\mu$, and therefore it is evident that cyclization occurred during treatment with benzoyl chloride and not during the original condensation.

When I was treated with 4-toluenesulfonyl chloride a tosyl derivative (IV) was obtained. Likewise when I was converted to the sodium alkoxide with sodium hydride and the alkoxide treated with tosyl chloride, the same substance, IV, was obtained.

The structure of IV as N-4-toluenesulfonyl-2phenyl-1,3-tetrahydrooxazine was demonstrated by hydrogenolysis of IV to N-(3-hydroxypropyl)-4toluenesulfonamide (V) which was also prepared from 3-aminopropanol and one equivalent of tosyl chloride. Thus 3-amino- or 3-benzylaminopropyl tosylate derivatives are not accessible by this route. The present observations, supported by the work of others,^{5b} who have shown that Schiff bases instead of oxazolines are produced from aldehydes and 1,2-aminoalcohols, lead us to suggest that the tetrahydro-1,3-oxazines reported to result from the reaction of 1,3-aminoalcohols, are, in fact, Schiff bases.

Another potential route to N-benzylazetidine is base-induced cyclization of N-3-benzamidopropyl benzoate (VI) or tosylate (VII), followed by re-

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Previous paper in this series, W. R. Vaughan, R. S.

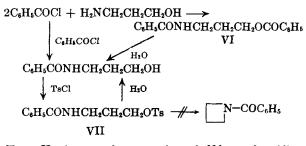
⁽²⁾ Hevious paper in this series, w. R. Vaugnan, R. S. Klonowski, R. S. McElhinney, and B. B. Millward, J. Org. Chem., 26, 138 (1961).

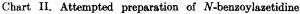
⁽³⁾ Abstracted from a portion of the Ph.D. dissertation of Robert Stephen Klonowski, University of Michigan, 1959.

⁽⁴⁾ A. I. Kiprianov and B. A. Raschkovan, J. Gen. Chem. U.S.S.R., 7, 1026 (1937) [Chem. Abstr., 31, 5356 (1937)].

⁽⁵a) G. E. McCasland and E. C. Horswill, J. Am. Chem. Soc., 73, 3923 (1951).

⁽⁵b) L. W. Daasch and U. E. Hanninen, J. Am. Chem. Soc., 72, 3673 (1950).





duction of benzovlazetidide (Chart II). To this end both compounds were prepared: VI by dibenzoylation of 3-aminopropanol; VII by tosylation of N-3-benzamidopropanol, prepared either by monobenzoylation of 3-aminopropanol or more satisfactorily by saponification of the ester group in VI. Upon hydrolysis of the tosyl group of VII followed by benzoylation VI was obtained, showing that no rearrangement takes place during tosylation, such as was encountered by Gabriel and Elfeldt.⁶ Both VI and VII were subjected to treatment with sodium ethoxide in refluxing ethanol, which cyclizes N-3-(4-toluenesulfonamido)propyl tosylate,³ but no reaction was detected with VI, while an oil (uncharacterized but showing characteristic benzamide absorption in the infrared) was obtained from VII. The considerably less acidic character of the N-benzamido as compared with the N-4toluenesulfonamido group as well as the lesser lability of benzoate compared with tosylate group is accountable for these results. Lithium aluminum hydride reduction of VII was not attempted, since it was to be expected that the anion of N-3benzylaminopropyl 4-toluenesulfonate would undergo further reactions, among which cyclization to N-benzylazetidine would be but one of several.

One further route to N-3-benzylaminopropyl tosylate was tentatively investigated. Ethylene cyanohydrin was treated with tosyl chloride and pyridine in chloroform at 0° to give a 72.5% yield of 3-(4-toluenesulfonoxy) propionitrile (β -cyanoethyl p-toluenesulfonate, VIII). It was our intention to reduce this substance to the corresponding amine and allow the amine to react with benzaldehyde. The reduction over Adams' catalyst in absolute ethanol at an initial hydrogen pressure of 53 p.s.i. was complete in seven hours, and a water soluble product was precipitated by the addition of dry ether to the evaporated solution. The solid was not allylamine 4-toluenesulfonate whose melting point it substantially depressed. Allylamine could not be extracted by ether from the aqueous solution of the solid after addition of alkali. However, upon distillation of the alkaline solution, allylamine was extracted from the distillate and isolated in the form of its picrate. From the original ether solution, from which the water soluble solid had been removed by filtration, there was isolated a very small quantity of ethylene di-4-toluenesulfonate, probably arising from traces of ethylene glycol in the ethylene cyanohydrin.

EXPERIMENTAL⁷

N-(3-Hydroxypropyl)benzaldimine (I). A solution of 37.6 g. (0.5 mole) of 3-aminopropanol and 53.1 g. (0.5 mole) of benzaldehyde in 150 ml. of dry benzene was refluxed until 9.5 ml. of water was collected in a water separator. The benzene was then distilled at atmospheric pressure, and the yellow oil was vacuum distilled. After a small forerun the product distilled at 118° (0.5 mm.): yield 73.5 g. (90%).

Anal. Calcd. for $C_{10}H_{13}NO: C, 73.59$; H, 8.03; N, 8.58. Found: C, 73.68; H, 8.06; N, 8.64.

The infrared spectrum possessed bands at 3360 cm.⁻¹ and 1650 cm.⁻¹ The ultraviolet spectrum showed an absorption maximum at 2467 Å with a molar extinction coefficient of 15,400.

N-Benzoyl-2-phenyl-1,3-tetrahydrooxazine (III). To a solution of 3.2 g. (0.02 mole) of N-(3-hydroxypropyl)benzaldimine in 15 ml. of pyridine (reagent grade) was added 2.8 g. (0.02 mole) of benzoyl chloride. Almost immediately a precipitate of pyridine hydrochloride appeared. The mixture was allowed to stand at room temperature for 15 min. and then poured into cold water to precipitate 2.4 g. of Nbenzoyl-2-phenyl-1,3-tetrahydrooxazine, m.p. 125.0-127.5°. Three recrystallizations from an acetone-water mixture gave the analytical sample, m.p. 127-128° (reported⁴ m.p. 127°).

Anal. Calcd. for $C_{17}H_{17}NO_2$: C, 76.40; H, 6.41; N, 5.24. Found: C, 76.97; H, 6.59; N, 5.20.

N-(p-Toluenesulfonyl)-2-phenyl-1,3-tetrahydrooxazine (IV). Procedure A. N-(3-Hydroxypropyl)benzaldimine (16.3 g., 0.1 mole) was dissolved in 70 ml. of pyridine (reagent grade), and the solution was cooled to -10° in an ice-salt bath. p-Toluenesulfonyl chloride (21.1 g., 0.11 mole) was added in portions keeping the temperature below 0°. After the addition the yellow solution was refrigerated (0°) for 2 hr. A precipitate of pyridine hydrochloride appeared either during the addition of p-toluenesulfonyl chloride or during the refrigeration period, after which the mixture was poured into 500 ml. of cold water.

The precipitated product was filtered, washed with cold 5% hydrochloric acid, followed by cold water, and then was air dried. The solid, 33.2 g., contained a large amount of adsorbed water which was removed by dissolving the solid in dry chloroform, separating the water layer, and drying the chloroform solution with anhydrous magnesium sulfate. Addition of petroleum ether (b.p. $30-60^{\circ}$) to the warm chloroform solution precipitated 22.8 g. (72%) of N-(p-toluenesulfonyl)-2-phenyl-1,3-tetrahydrooxazine, m.p. 141-143°. Two recrystallizations from dry ether gave the analytical sample, m.p. 145.5-146.0°.

Anal. Calcd. for $C_{17}H_{19}NO_3S$: C, 64.32; H, 6.03; N, 4.41. Found: C, 64.32; H, 6.04; N, 4.27.

Procedure B. A solution of 16.3 g. (0.100 mole) of N-(3hydroxypropyl)benzaldimine in 150 ml. of dry ether was stirred for 16 hr. with 2.4 g. (0.10 mole) of sodium hydride. A solution of 19.1 g. (0.100 mole) of p-toluenesulfonyl chloride in 75 ml. of dry ether was added dropwise and the solution was refluxed for 1 hr. Forty milliliters of water was added and the layers were separated. The ether layer was dried with magnesium sulfate and distilled at atmospheric pressure to give a brown oil. The latter was dissolved in hot acetone and, on cooling, N-(p-toluenesulfonyl)-2-

⁽⁶⁾ S. Gabriel and P. Elfeldt. Ber., 24, 3213 (1891).

⁽⁷⁾ All melting and boiling points are uncorrected. Microanalyses by Spang Microanalytical Laboratory, Ann Arbor, Mich. The infrared spectra of solids were recorded from Nujol mulls on a Perkin-Elmer Model 21 infrared spectrophotometer; liquids were recorded as thin films by the same instrument.

phenyl-1,3-tetrahydrooxazine crystallized; yield, 25.2 g. (80.5%), m.p. 143-145° which was unchanged on admixture with the compound prepared by Procedure A.

N-(3-Hydroxypropyl)-p-toluenesulfonamide (V). Procedure N-(p-toluenesulfonyl)-2-phenyl-1,3-tetrahydrooxazine Α. (IV) (1.58 g., 5 mmoles) was dissolved in 75 ml. of absolute ethanol which had been saturated with dry hydrogen chloride. A mixture of 0.1 g. of Adams' catalyst and 2 ml. of ethanol was added and the mixture hydrogenated at 1 atm. of hydrogen pressure. The absorption of hydrogen stopped after 4 hr. The catalyst was removed by filtration and the solution was evaporated to dryness under reduced pressure (water-aspirator). The solid was recrystallized from ether giving 1 g. (87%) of N-(3-hydroxypropyl)-p-toluenesul-fonamide, m.p. 55-57°. Two recrystallizations from a mixture of dry chloroform and petroleum ether (b.p. 30-60°) gave the analytical sample, m.p. 55-56°.

Anal. Calcd. for C₁₀H₁₅NO₃S: C, 52.39; H, 6.59; N, 6.11; S, 13.97. Found: C, 52.07; H, 6.41; N, 5.88; S, 13.88.

Procedure B. p-Toluenesulfonyl chloride (19.1 g., 0.100 mole) was added in small portions to a cold solution of 7.5 g. (0.10 mole) of 3-aminopropanol in 15 ml. of pyridine. The temperature was kept below 3° during the addition. After refrigeration (0°) for 1 hr. the mixture was poured into 100 ml. of ice-water. The oil that separated was dissolved in chloroform and this was washed with cold, dilute hydrochloric acid and water. After drying with magnesium sulfate, the solution was cooled and diluted with petroleum ether (b.p. 30-60°). The product, 20.5 g. (83.7%), crystallized slowly, m.p. 52-55°. A mixed melting point with the product prepared by Procedure A showed no depression.

N-(3-Hydroxypropyl)benzamide. Procedure A. To 75.1 g. (1.0 mole) of 3-hydroxypropylamine 70.3 g. (0.5 mole) of benzoyl chloride was slowly added. The mixture was then warmed on a steam bath for 0.5 hr. and, after cooling to room temperature, was extracted with chloroform. The chloroform solution was distilled at atmospheric pressure to remove the solvent and then was vacuum distilled to give 45 g. (50%) of product, b.p. 198° (1.5 mm.), $n_{\rm D}^{21}$ 1.5590. The phenylurethan melts at 118–120°.

Anal. Calcd. for C17H18N2O3: C, 68.46; H, 6.08; N, 9.39. Found: C, 68.55; H, 6.00; N, 9.20.

Procedure B. A solution of 56 g. (0.2 mole) of 3-benzamidopropyl benzoate and 8 g. (0.2 mole) of sodium hydroxide in 500 ml. of water was refluxed for 1.5 hr., after which the homogeneous solution was continuously extracted with chloroform for 8 hr. The chloroform solution was dried with magnesium sulfate and distilled, first at atmospheric pressure to remove the solvent, and then in vacuo. After a very small forerun, the product distilled at 196-200° (mostly at 198°) (1.5 mm.); yield, 20 g. (57.2%). The infrared spectruin was superimposable with the spectrum of N-(3-hydroxypropyl)benzamide prepared by Procedure A. During the distillation the compound crystallized to a solid, m.p. 60-61° [reported⁸ for N-(3-hydroxypropyl)benzamide, m.p. 60.0-60.5° l.

3-Benzamidopropyl benzoate (VI). Procedure A. A solution of 75.1 g. (1.0 mole) of 3-hydroxypropylamine in 200 g. of pyridine was cooled to 0° and 285 g. (2 moles) of benzoyl chloride was added in portions. The temperature was allowed to fluctuate between 0° and 80°. After the addition the solution was heated on a steam bath for 0.5 hr. and allowed to stand at room temperature for 2 hr. Dilution with ice and 5% hydrochloric acid gave the product, m.p. 83-84°, after recrystallization from aqueous ethanol: yield, 255.7 g. (90%)

Anal. Caled. for C17H17NO3: C, 72.07; H, 6.05; N, 4.94. Found: C, 71.90; H, 6.02; N, 5.08.

Procedure B. To a solution of 1.8 g. (10 mmoles) of N-(3-hydroxypropyl)benzamide in 5 ml. of pyridine (reagent grade) was added 1.4 g. (10 mmoles) of benzovl chloride. During the exothermic reaction that followed pyridine

(8) S. Gabriel, Ann., 409, 326 (1915).

hydrochloride precipitated. The mixture was poured onto ice when it cooled to room temperature, and the oil which separated solidified on standing. After filtering, the solid was washed with water, dilute hydrochloric acid, and again with water. Recrystallization from a chloroform-petroleum ether (b.p. $30-60^{\circ}$) mixture gave 1.7 g. (60.5%) of 3-benz-amidopropyl benzoate, m.p. $83-85^{\circ}$. No depression of the melting point was observed on admixture with an authentic sample from Procedure A.

 $\label{eq:s-Benzamidopropyl p-toluenesulfonate (VII). Procedure \ A.$ A solution of 16.5 g. (0.093 mole) of 3-benzamidopropanol in 15 ml. of pyridine was cooled to 0° and 18.0 g. (0.093 mole) of p-toluenesulfonyl chloride was added in portions, keeping the temperature below 3°. The yellow solution was refrigerated (0°) for 2 hr. during which time white crystals of pyridine hydrochloride appeared. To this mixture was slowly added 100 ml. of ice-water. The product, which crystallized immediately, was filtered and washed with cold, dilute hydrochloric acid. The adsorbed water was removed by recrystallization from chloroform: yield, after recrystallization, 18.7 g. (60.5%), m.p. 156.5-157.0°. Anal. Caled. for C₁₈H₂₁NO₄S: C, 61.24; H, 5.74; N, 4.20;

S, 9.62. Found: C, 61.31; H, 5.78; N, 4.29; S, 9.71.

Procedure B. Benzoyl chloride (14.0 g., 0.1 mole) was added to 15.0 g. (0.2 mole) of 3-hydroxypropylamine. The resulting solution was heated on the steam bath for 1 hr. and then was extracted with dry chloroform. To the chloroform solution was added 8 g. (0.1 mole) of pyridine and, after cooling to 0° , 19.1 g. (0.1 mole) of *p*-toluenesulfonyl chloride in small portions. After keeping the solution at 0° for 2 hr. it was extracted with ice-water. The chloroform solution was dried with magnesium sulfate and the solvent removed at reduced pressure. The resulting oil was dissolved in a small amount of absolute ethanol and the solution was diluted with petroleum ether (b.p. 60–75°) to give 13.5 g. (40.5%) of product, m.p. 143-147°. Recrystallization from chloroform gave a product which melted at 154-156°. A mixed melting point with the product obtained in Procedure A showed no depression.

Attempted cyclization of 3-benzamidopropyl benzoate. A solution of 0.23 g. (0.01 g.-atom) of sodium in 100 ml. of absolute ethanol was added to a solution of 2.8 g. (0.01 mole) of 3-benzamidopropyl benzoate (VI) in 100 ml. of absolute ethanol. The solution was refluxed for 4 hr. after which the solvent was removed under reduced pressure. The residue was extracted with ether. The solid remaining after the extraction was dissolved in water and acidified with dilute hydrochloric acid. No precipitation occurred.

The ethereal solution was concentrated and, on cooling, 2.3 g. of 3-benzamidopropyl benzoate precipitated, m.p. 80-82°. A mixed melting point with the starting material showed no depression.

Attempted cyclization of 3-(p-toluenesulfonamido)propyl benzoate. The above procedure was followed substituting 3.3 g. (0.01 mole) of 3-(p-toluenesulfonamido)propyl benzoate (VII) for 3-benzamidopropyl benzoate (VI). The ethereal extract of the solid remaining after the solvent had been removed contained an oil whose infrared spectrum showed absorption bands similar to those of the starting material. Crystallization did not occur on seeding with the starting material.

 β -Cyanoethyl p-toluenesulfonate (VIII). A solution of 14.2 g. (0.2 mole) of ethylene cyanohydrin and 40 g. of pyridine in 75 ml. of chloroform was stirred and cooled in an ice-bath, and a solution of 36.0 g. (0.2 mole) of ptoluenesulfonyl chloride in 100 ml. of chloroform was added dropwise. The solution was stirred for 2 hr. and diluted with dilute hydrochloric acid. The chloroform layer was separated and evaporated in a stream of air to a white semisolid. Recrystallization from ethanol-water yielded 32.6 g. (72.5%) of β -cyanoethyl *p*-toluenesulfonate, m.p. 64-65

Anal. Caled. for C16H11NO3S: C, 53.30; H, 4.92; N, 6.22; S, 14.23. Found: C, 53.58; H, 4.99; N, 6.04; S, 14.23.

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Reduction of VIII. A warm solution of 13 g. (0.05 mole) of VIII in 200 ml. of absolute ethanol containing 0.5 g. of Adams' catalyst was hydrogenated on a Parr shaker. The initial hydrogen pressure was 53 p.s.i. The solution absorbed 9.5 lb. of hydrogen in 7 hr. There was no additional absorption in the next 15 hr. The catalyst was filtered and the solvent was removed from the filtrate under reduced pressure. The addition of dry ether to the residue precipitated 12.0 g. of white solid, m.p. $350-352^{\circ}$ dec.

Anal. C, 45.06; H, 6.01; N, 7.72; S, 18.29. The solid was soluble in water and when the aqueous solution was made basic an ammoniacal odor was detected. No amine, however, was extracted with ether. An aqueous solution was made strongly alkaline with potassium hydroxide and the solution distilled up to 100°. The distillate was saturated with potassium hydroxide and extracted with ether. To the ether solution, after drying with magnesium sulfate, was added a saturated ether solution of picric acid. Allylamine picrate, m.p. 135-140°, precipitated immediately. A mixed melting point with an authentic sample of allylamine picrate showed no depression.

From the ether solution there was obtained 0.33 g. of ethylene glycol di-p-toluenesulfonate, m.p. 120-121° (reported⁹ m.p. 125-126°). A sample of ethylene glycol di-ptoluenesulfonate was prepared by the reaction of p-toluenesulfonyl chloride with ethylene glycol in pyridine solution. The melting point was 123-125°. A mixture of the two solids melted at 123-125°.

ANN ARBOR, MICH.

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[CONTRIBUTION FROM THE DEPARTMENT OF BIOLOGICAL SCIENCES, STANFORD RESEARCH INSTITUTE]

Potential Anticancer Agents.¹ XLIII. Analogs of Chlorambucil. IV.² Synthesis of Isochlorambucil and Related Benzylic Type Alkylating Agents

W. A. SKINNER, ABELARDO P. MARTINEZ, HELEN F. GRAM, LEON GOODMAN, AND B. R. BAKER

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p-[Bis(2-chloroethyl)aminomethyl]hydrocinnamic acid (XIII) (isochlorambucil), an isomer of chlorambucil containing the more chemically reactive benzylic type alkylating group, has been synthesized for evaluation as an anticancer agent. Several related monofunctional alkylating agents have also been synthesized for test evaluation, namely p-(2-chloroethylhiomethyl)-hydrocinnamic acid (II), p-[(2-chloroethyl)ethylaminomethyl]hydrocinnamic acid (IVb), methyl p-(1-aziridinylmethyl) hydrocinnamate (VIII), and p-[(2-chloroethyl)aminomethyl]hydrocinnamic acid (XIVb).

Chlorambucil,³ 4-*p*-[bis(2-chloroethyl)amino] phenylbutyric acid, is one of the most useful alkylating agents in the clinic.⁴ Although chlorambucil is highly effective against the Walker rat Sarcoma 256, it shows little activity against Sarcoma 180, Adenocarcinoma 755, or Leukemia L-1210 in the mouse. As part of the continuing search for analogs of chlorambucil^{2,5,6} that may have a different tumor spectrum^{4,7} or may be more efficacious in man, this paper describes a series of chlorambucil analogs wherein the alkylating function is separated from the benzene ring by a methylene group such as in Compound XIII. Since aliphatic mustards are chemically more reactive than the corresponding aryl mustards, a change in tumor spectrum or efficiency or both might be anticipated. In addition, some of the monofunctional alkylating agents of this more reactive benzylic type (such as II, IVb or XIVb) described in this paper might be irreversible enzyme inhibitors.^{8,9}

Chloromethylation of hydrocinnamic acid with aqueous formaldehyde and hydrochloric acid by the method of Bogdanov¹⁰ afforded p-(chloromethyl)hydrocinnamic acid (VI) in 50% yield. Milder conditions of chloromethylation, namely chloromethyl methyl ether and stannic chloride, were without effect on hydrocinnamic acid since the latter was recovered unchanged. Fisher esterification of VI with methanolic hydrogen chloride

⁽¹⁾ This program is under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Public Health Service, Contract SA-43-ph-1892. The opinions expressed in this paper are those of the authors and not necessarily those of the Service Center. For the preceding paper of this series, cf. J. DeGraw, L. Goodman, and B. R. Baker, J. Org. Chem. in press.

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