Thallium(I) salt of N-phthaloyl-L-leucine was obtained in 78.5% yield, mp 197–198°.

Anal. Calcd for $C_{14}H_{14}NO_4Tl$: C, 36.19; H, 2.97; N, 3.02. Found: C, 36.14; H, 3.38; N, 3.22.

1-Acyl- (or -Sulfonyl-) oxy-2(1H)-pyridones (2). Method A. From 1 and Acyl or Sulfonyl Halides.—The thallium salt 1 (5 mmol) was suspended in 100 ml of anhydrous ether and an equimolar quantity of the acyl or sulfonyl halide was added. The mixture was stirred for 30 min at room temperature and filtered and the filtrate was evaporated. The residue was suspended in petroleum ether to which a small amount of ethyl acetate (10%) had been added; filtration then gave the pure products[11] in practically quantitative yield.

Method B. From Thallium(I) Carboxylates.—A suspension of 1-hydroxy-2(1H)-pyridone (2 g) in 20 ml of thionyl chloride was stirred at room temperature for 20 min with exclusion of moisture. Some 1-hydroxy-2(1H)-pyridone hydrochloride, mp 113–134° dec, was filtered off and the filtrate was evaporated. Excess thionyl chloride was removed by keeping the sample for 10 min *in vacuo* (16 mm) and the residual brown syrup was dissolved in 25 ml of anhydrous tetrahydrofuran. The thallium(I) carboxylate (0.9 equiv, based on the assumption[12] that the syrup constituted pure chlorosulfite **3**, mol wt 193) was added and the mixture was stirred vigorously for 30 min at ambient temperature. Thallium(I) chloride was then filtered off and washed well with anhydrous tetrahydrofuran, the combined filtrates were evaporated, the residue was taken up in 15 ml of anhydrous ethyl acetate, and the solution was left at 5° for several hours. After some insoluble material had been removed by filtration, the 1-acyloxy-2(1H)-pyridone crystallized from the evaporated filtrate on scratching. Stirring in ethyl acetate–petroleum ether followed by filtration gave the crude product, which was purified by crystallization from ethyl acetate. Yields of the various active esters prepared in this way are listed in Table I.

Acetylglycylglycine Ethyl Ester (4).—The chlorosulfite **3** (2.50 g, 13 mmol) was obtained from 2.70 g of 1-hydroxy-2(1H)-pyridone as described above (method B) and dissolved in 25 ml of anhydrous tetrahydrofuran. To the stirred solution was added 3.85 g (12 mmol) of thallium(I) acetylglycinate and stirring was continued for 30 min. After the precipitated thallium(I) chloride had been filtered off, glycine ethyl ester (1.24 g, 12 mmol) and 5 drops of triethylamine were added and the mixture was stirred at room temperature for 2.5 hr. A small amount of solid material was removed by filtration and the filtrate was evaporated to yield a syrup which was dissolved in 20 ml of water. The aqueous solution was passed through a column containing (lower half) of 10 g of Dowex 50W-X4 (H^+) and (upper half, separated by a plug of glass wool) 10 g of Dowex 21K (OH^-). The column was thoroughly washed with water and the combined eluates were evaporated. Two coevaporations with absolute ethanol followed by treatment with activated charcoal gave 1.02 g (42%) of a colorless solid, mp 139–141°. Recrystallization from absolute ethanol raised the melting point to 147–148° (lit. mp 152[13] and 150°[14]). The nmr spectrum (in D_2O) confirmed structure **4**.

N-Acetyl-DL-alanylglycine Ethyl Ester (5).—The dipeptide **5** was obtained from **3**, the thallium(I) salt of N-acetyl-DL-alanine, and glycine ethyl ester, in a similar manner to that described for the synthesis of **4**. Crystallization of the crude product, mp 109–111°, from chloroform–petroleum ether gave pure material, mp 113–115°, yield 29%.

Anal. Calcd for $C_9H_{16}N_2O_4$: C, 49.98; H, 7.46; N, 13.25. Found: C, 49.64; H, 7.29; N, 13.08.

The nmr spectrum of **5** ($CDCl_3$) showed a triplet at τ 8.73 (3 H), a doublet at 8.60 (3 H), a singlet at 8.00 (3 H), a singlet at 6.02 (2 H), a quartet at 5.80 (2 H), and a quartet at 5.38 (1 H).

N-Phthaloyl-L-leucine Anilide (6).—The chlorosulfite **3** (1.0 g, 5.2 mmol) was dissolved in 20 ml of anhydrous tetrahydrofuran and 1.57 g (4.65 mmol) of the thallium(I) salt of N-phthaloyl-L-leucine added. The mixture was stirred at room temperature for 1 hr, then, without filtration, aniline (510 mg, 5.5 mmol) was added, and stirring was continued for 2 hr. The syrup which was obtained after filtration and evaporation was dissolved in methylene chloride (60 ml), the solution was extracted twice with 20-ml portions of a 5% aqueous sodium bicarbonate solution, the organic layer was dried over anhydrous sodium sulfate, treated with activated charcoal, and filtered, and the filtrate was evaporated. The residue was dried *in vacuo* to give 970 mg of crude product, mp 130–135°. Crystallization from benzene–petroleum ether gave 795 mg (51%) of beautiful needles, mp 154–155°, $[\alpha]D$ −21° (*c* 0.9, glacial acetic acid).[15]

1-Acetoxy-2(1H)-pyridone (2, R = CH_3).—2-Bromopyridine 1-oxide (**8**) hydrochloride (1.2 g, 6.1 mmol) was suspended in 10 ml of anhydrous tetrahydrofuran and 10 g of sodium bicarbonate was added. The slurry was mixed well and filtered after 10 min; the residue was thoroughly washed with tetrahydrofuran. The volume of the filtrate was then approximately 50 ml. Thallium(I) acetate (1.6 g, 6.1 mmol) was added together with 10 ml of glacial acetic acid [to dissolve the thallium(I) salt] and 5 ml of acetic anhydride (to remove traces of water). The clear solution was then heated under reflux; after 30 min a fine precipitate of thallium(I) bromide started to separate. Heating was continued for 18 hr, thallium(I) bromide (1.19 g, 66.9%) was removed by filtration, and the filtrate was evaporated. The syrupy residue was dissolved in anhydrous ethyl acetate and unreacted insoluble thallium(I) acetate was removed by filtration. Addition of petroleum ether resulted in slow crystallization of 510 mg (59%) of **2** (R = CH_3), mp 92–93°. Recrystallization from ethyl acetate–petroleum ether gave beautiful prisms, mp 94–95° (lit.[4] mp 93–94°).[16]

2-Chloropyridine 1-oxide (**7**) under the same conditions gave (R = CH_3) in 58% yield.

Registry No.—Thallium (I) salt of acetylglycine, 23715-40-4; thallium (I) salt of N-acetyl-DL-alanine, 23715-41-5; thallium (I) salt of N-phthaloyl-L-leucine, 23715-42-6; **1**, 23715-39-1; **4**, 3757-98-0; **5**, 23595-74-6.

(11) Identity and purity were determined by comparison of physical data (melting point and ir and uv spectra) with reported values.[4]

(12) Attempted purification of this syrup led to extensive decomposition. We assume that it is the N-chlorosulfite **3** rather than N-chloro-2(1H)-pyridone because reaction with the thallium(I) carboxylate results in vigorous evolution of sulfur dioxide. Gas evolution is almost explosive in the absence of solvent, but is readily controlled if the N-chlorosulfite is dissolved in tetrahydrofuran before the thallium(I) carboxylate is added.

(13) E. Fischer, *Chem. Ber.*, **35**, 1095 (1902).

(14) R. G. Petrova, L. N. Akinova, and N. I. Gavrilov, *Zh. Obshch. Khim.*, **24**, 2239 (1954).

(15) J. C. Sheehan, D. W. Chapman, and R. W. Roth [*J. Amer. Chem. Soc.*, **74**, 3822 (1952)] reported mp 154.5–156°, $[\alpha]D$ −21° (acetic acid).

(16) Uv and ir spectra were also identical with the reported values.[4]

The Addition of N-Bromosuccinimide to 3-Sulfolene

J. M. LANDESBERG AND M. SIEGEL

Adelphi University, Garden City, New York 11530

Received November 13, 1969

The use of N-bromosuccinimide (NBS) as an allylic brominating agent has been known for some time and has enjoyed wide applicability.[1] A lesser known, but not entirely unknown, reaction of NBS is the addition of this reagent to the double bond.[1b,2-4] This latter process is usually observed when electron-withdrawing groups[3] or steric factors[2] make stabilization of the allylic radical difficult. Succinimido radicals have been suggested.[2,3]

In connection with the above, we have reexamined the reaction of NBS with 2,5-dihydrothiophene-1,1-dioxide (3-sulfolene, **1**). Backer, *et al.*,[5] reported that

(1) (a) C. Djerassi, *Chem. Rev.*, **43**, 271 (1948); (b) L. Horner and E. H. Winkelmann, *Angew. Chem.*, **71**, 349 (1959).

(2) L. H. Zalkow and C. D. Kennedy, *J. Org. Chem.*, **29**, 1290 (1964), and references cited therein.

(3) W. J. Bailey and J. Bello, *ibid.*, **20**, 525 (1955).

(4) J. R. Shelton and C. Ciadella, *ibid.*, **23**, 1128 (1958).

(5) H. J. Backer, W. Stevens, and N. Dost, *Rec. Trav. Chim. Pays-Bas*, **67**, 451 (1948); *Chem. Abstr.*, **43**, 558 (1948).

the reaction of these reagents in CCl_4, both with or without the addition of benzoyl peroxide (or ultraviolet irradiation), led to the recovery of starting material along with 3,4-dibromosulfolane and succinimide. The lack of any allylic bromination product suggested a destabilizing influence from the sulfone. One might then anticipate addition to the double bond, and the presence of adduct in the reaction mixture was sought.

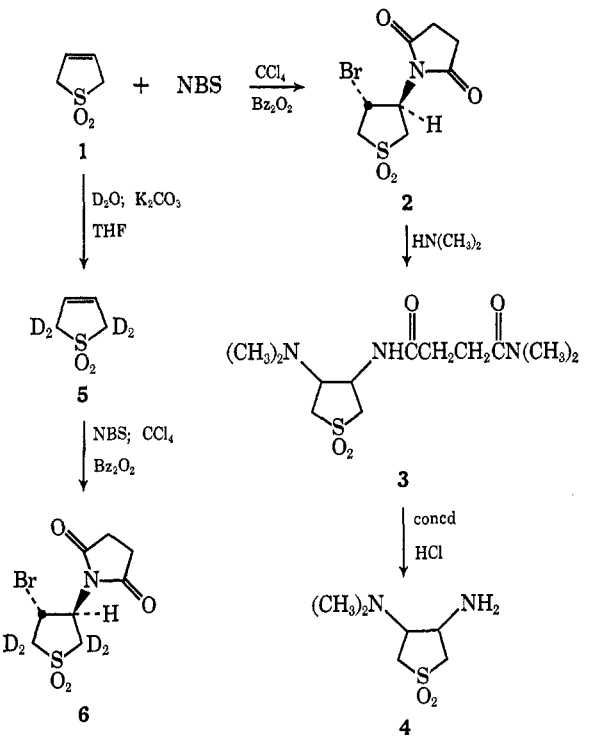
When **1** and NBS are heated in CCl_4 in the presence of benzoyl peroxide, as Backer describes, a solid separates. Examination of this solid by tlc showed the presence of succinimide and a second component which was found to be a 1:1 adduct. Spectral data confirmed the gross structure of the adduct as **2**. An attempt to form the adduct without any benzoyl peroxide in solution was unsuccessful; only the products reported by Backer were isolated.[5]

The positions of substitution and the geometry of the substituents at these positions were established by the nmr spectrum of the adduct **6** obtained from NBS addition to 2,2,5,5-tetradeuteriothiophene 1,1-dioxide (**5**).[6] The nmr spectrum of **6** shows a two-proton signal centered at δ 5.10 for the protons at C_3 and C_4, compared with the chemical shift of analogous protons of 3,4-dibromosulfolane at δ 4.85–5.10 (m).[7] The δ 5.10 absorption could be resolved into two signals with a separation of only 2 cps. The lack of any significant coupling constant is consistent with a *trans*-substitution pattern on a five-membered ring.[8] Thus, the 3-bromo and 4-succinimido groups are situated *trans* in the five-membered sulfone ring.

While the mechanism of addition is not known with certainty, the fact that the reaction only takes place when benzoyl peroxide is present is suggestive of a free-radical process[2] rather than one of polar addition. The intermediacy of succinimido radicals is implied.[9] This reaction is analogous to one observed by Kharasch, *et al.*[10] Here bromotrichloromethane ($BrCCl_3$) reacts with 3-sulfolene in the presence of peroxides to yield 3-bromo-4-(trichloromethyl)sulfolane in a free-radical process.

Further transformations of **2** were possible. Thus dimethylamine displaced bromine and opened the succinimide ring; concentrated hydrochloric acid hydrolyzed the side chain and led to diamine **4**. Scheme I summarizes these reactions.

SCHEME I



Experimental Section

General.—All melting points were taken on a Thomas–Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were taken on a Perkin-Elmer grating infrared spectrophotometer, Model 257. The 1601-cm^{-1} peak of polystyrene is used as the reference standard. Nuclear magnetic resonance spectra were measured on a Varian A-60, with chemical shifts recorded in δ units downfield from tetramethylsilane. Microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

***trans*-3-Bromo-4-succinimidotetrahydrothiophene 1,1-Dioxide (2).**—2,5-Dihydrothiophene 1,1-dioxide (20.0 g, 0.169 mol), N-bromosuccinimide (33.2 g, 0.188 mol), and benzoyl peroxide (1.00 g) were refluxed in carbon tetrachloride (500 ml) for 12 hr. The solution was then cooled to room temperature and filtered. The solid material was stirred with chloroform (100 ml) for 15 min before filtering; this yielded 3.90 g (7.8%) of **2**, mp 217–218.5°. A single recrystallization from methanol raised the melting point to 218–219°.

Anal. Calcd for $C_8H_{10}BrNO_4S$: C, 32.44; H, 3.40; N, 4.73; Br, 26.98; S, 10.83. Found: C, 32.59; H, 3.28; N, 4.69; Br, 26.85; S, 10.84.

The spectral characteristics of **2** are as follows: ir (Nujol) 1700 (broad, amide C=O), 1315 (broad, SO_2), 1130, and 1145 cm^{-1} (strong, SO_2); nmr (DMSO-d_6) δ 5.30–4.75 [m, 2, $-CH(Br)CH(N<)-$], 4.08–3.40 (m, 4, $-CH_2SO_2CH_2-$), and 2.73 [s, 4, $-C(O)CH_2CH_2C(O)-$].

N-[4-(3-Dimethylaminotetrahydrothiophene 1,1-dioxide)]-N′,N′-dimethylsuccinimide (3).—Compound **2** (7.94 g, 26.8 mmol) was slowly added as a solid to a cooled, stirred solution of dimethylamine (48.8 g, 1.08 mol) in benzene (265 ml). This mixture was then stirred for 3 days at room temperature. The solution was then filtered, excess dimethylamine was removed under vacuum, and the remaining benzene solution was washed with 15% hydrochloric acid. The aqueous phase was washed with chloroform, cooled, and neutralized with concentrated sodium hydroxide. This was washed with chloroform, and the combined chloroform extracts were dried ($MgSO_4$) and concentrated while the temperature was maintained below 30°. An oil remained. The oil, when taken up in benzene–ether, deposited crystals, mp 142–143°. Recrystallization from ethyl acetate gave 74 mg (9%) of **3**, mp 143.5–144.5°.

Anal. Calcd for $C_{12}H_{23}N_3O_4S$: C, 47.19; H, 7.59; N, 13.76. Found: C, 46.92; H, 7.75; N, 13.60.

The spectral characteristics of **3** are as follows: ir (Nujol) 3240 (broad, NH), 1620 (broad, amide C=O), 1340, 1150, and 1130 cm^{-1} (strong, SO_2); nmr ($CDCl_3$) δ 7.33–7.0 (broad, 1, –NH–), 4.85–4.23 [m, 1, $-CH(NH-)-$], 3.90–3.08 [m, 5, $-CH_2-SO_2CH_2CH(N<)-$], 3.03, 2.95, [s, 6, $O=CN(CH_3)CH_3$], 2.60 [s, 4, $-C(O)CH_2CH_2C(O)-$], and 2.33 [s, 6, $-N(CH_3)_2$].

3-Amino-4-dimethylaminotetrahydrothiophene 1,1-Dioxide (4).—Compound **3** (245 mg, 0.802 mmol) was refluxed in concentrated hydrochloric acid (10 ml) for 12 hr. The solution was then washed with chloroform; the aqueous phase was cooled, neutralized with concentrated sodium hydroxide, and washed with chloroform. The chloroform extract was dried ($MgSO_4$)

(6) D. S. Weinberg, C. Stafford, and M. W. Scoggins, *Tetrahedron*, **24**, 5409 (1968).

(7) "The Sadtler Standard Spectra," Vol. 2, Sadtler Research Laboratories, Philadelphia, Pa., Spectrum No. 586.

(8) J. R. Dyer, "Applications of Absorption Spectroscopy of Organic Compounds," Prentice-Hall, Inc., Englewood Cliffs, N. J., 1965, p 117.

(9) T. R. Beebe and F. M. Howard [*J. Amer. Chem. Soc.*, **91**, 3379 (1969)] have demonstrated the intermediacy of succinimido radicals.

(10) M. S. Kharasch, M. Freiman, and W. H. Urry, *J. Org. Chem.*, **13**, 570 (1948).

and concentrated to yield an oil. This oil was taken up in ether, an equal volume of petroleum ether (bp 30–60°) was added, and the solution was cooled; 70 mg (49%) of **4** separated, mp 79–80.5°.

Anal. Calcd for $C_6H_{14}N_2O_2S$: C, 40.43; H, 7.92; N, 15.72. Found: C, 40.25; H, 7.95; N, 15.43.

The spectral characteristics of **4** are as follows: ir (Nujol) 3360 (strong, NH), 1350, 1160, 1135, and 1120 cm^{-1} (strong, SO_2); nmr ($CDCl_3$) δ 3.80–2.67 (m, 6, ring protons), 2.33 [s, 6, $-N(CH_3)_2$], and 1.67 (broad, 2, $-NH_2$).

2,2,5,5-Tetradeuteriothiophene 1,1-Dioxide (5).—This compound was prepared according to the method of Weinberg, *et al.*[6] 2,5-Dihydrothiophene 1,1-dioxide (1.18 g, 9.98 mmol) was dissolved in tetrahydrofuran (10 ml); to this solution was added deuterium oxide (20.4 g, 99.7%, Merck Sharp and Dohme of Canada, Ltd.) and anhydrous potassium carbonate (0.5 g). The mixture was stirred for 2 days at room temperature. Solvent was removed under vacuum. Deuterium oxide (13 g) and tetrahydrofuran (7 ml) were added and the procedure was repeated. Solvent was then removed. The residue was triturated with chloroform, and the chloroform was dried ($MgSO_4$), filtered, and evaporated to yield 0.945 g (77.5%) of **5**, mp 63–64°. The nmr spectrum showed greater than 95% deuterium incorporation: nmr ($CDCl_3$) δ 6.05 (s).

***trans*-3-Bromo-3,4-dihydro-4-succinimido-2,2,5,5-tetradeuteriothiophene 1,1-Dioxide (6).**—Compound **5** (820 mg, 6.71 mmol), N-bromosuccinimide (670 mg, 3.76 mmol) and benzoyl peroxide (570 mg) were refluxed in carbon tetrachloride (15 ml) for 3 hr. The solution was then cooled and filtered. The collected solid material was taken up in chloroform and the solution was filtered. The filtrate was concentrated, methanol was added and heated, and the hot solution was filtered. Upon cooling, the filtrate deposited light yellow crystals. Recrystallization from methanol gave white needles: mp 214–215°; nmr (DMSO-d_6) δ 5.10 (two resolved signals which are separated by 2 cps, two hydrogens on C_3 and C_4) and 2.77 [s, 4, $-C(O)CH_2CH_2C(O)-$].

Registry No.—**1**, 77-79-2; **2**, 23740-31-0; **3**, 23740-32-1; **4**, 23740-33-2; **5**, 20966-34-1; **6**, 23829-44-9; N-bromosuccinimide, 128-08-5.

Acknowledgment.—We are grateful to the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research (Grant 1061-G).

Potential Folic Acid Antagonists. IV. Synthetic Approaches to Analogs of Aminopterin and Methotrexate. IV. The Preparation of *p*-{[(2,4-Diamino-6-pteridinyl)methyl]amino}-benzoic Acids[1,2]

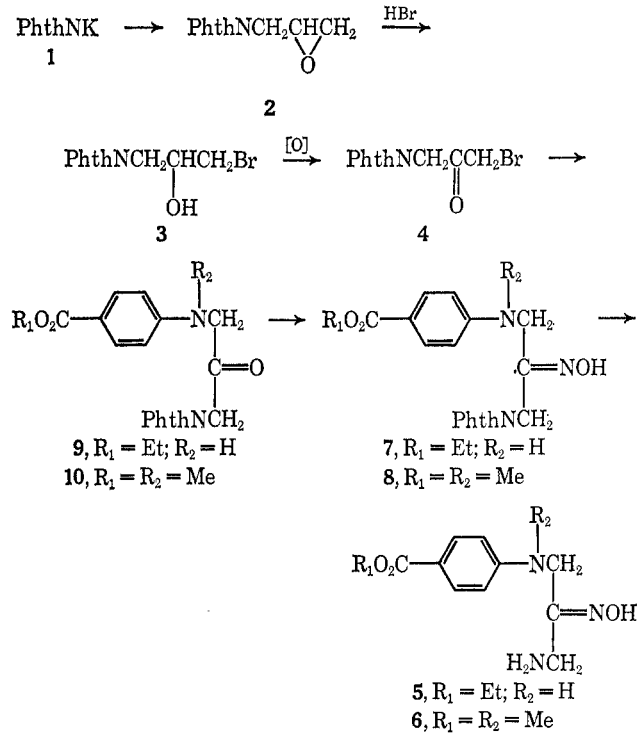
ROBERT D. ELLIOTT, CARROLL TEMPLE, JR., AND JOHN A. MONTGOMERY

Kettering-Meyer Laboratory, Southern Research Institute, Birmingham, Alabama 35205

Received October 27, 1969

As part of our program on the synthesis of folic acid antagonists, methods were needed for the construction of the pyrazine ring containing the *p*-(methyleneamino)-benzoyl moiety of folic acid, and of its analogs aminopterin and methotrexate. Although the preparation of the pteroic acid analogs **21**[3] and **23**[4] by the reaction of 2,4,5,6-tetraaminopyrimidine with a *p*-aminobenzoic acid in the presence of a halogenated three-carbon aldehyde or ketone has been reported, the former was obtained in a crude mixture and the latter as a dihydrate in unspecified yield. This method of preparation is unattractive in that the desired product is obtained in low yield and is difficult, if not impossible, to purify. Previously, Boon and Leigh[5] developed an unambiguous route to 6-substituted pteridines that involved the reduction of [(5-phenylazo-4-pyrimidinyl)amino]acetones. However, the synthesis by this method of a 6-(phenoxymethyl)pteridine for use as an intermediate for the preparation of compounds like **21** and **23** was unsuccessful when the phenoxy group underwent reductive cleavage. We report the preparation of some *p*-{[(2,4-diamino-6-pteridinyl)methyl]amino}benzoic acids by a modification of the Boon and Leigh procedure, which will also be used to prepare other analogs in which the pyrimidine ring has been replaced with the pyridine ring to give the corresponding 1- and 3-deazapteridine ring systems.

The intermediate N-3-(bromoacetonyl)phthalimide (**4**) was prepared in three steps in 24% yield from potassium phthalimide (**1**) *via* **2** and **3**.[6] Alkylation of



Phth = phthaloyl

ethyl *p*-aminobenzoate and methyl *p*-(methylamino)-benzoate,[7] respectively, with the bromo ketone **4** gave the diaminoacetones **9** (72%) and **10** (34%). The condensation of these keto compounds with $NH_2OH \cdot HCl$ in a refluxing mixture of pyridine and EtOH gave the corresponding oximes **7** (43%) and **8** (72%), both isolated as a mixture of the *syn* and *anti* isomers. The

(1) This work was supported by funds from the C. F. Kettering Foundation, and Chemotherapy, National Cancer Institute, National Institutes of Health, Contract No. PH43-64-51.

(2) For a related paper in this series, see R. D. Elliott, C. Temple, Jr., and J. A. Montgomery, *J. Org. Chem.*, **33**, 533 (1949).

(3) D. R. Seeger, U. S. Patent 2,568,597 (1947).

(4) D. R. Seeger, D. B. Cosulich, J. M. Smith, Jr., and M. E. Hultquist, *J. Amer. Chem. Soc.*, **71**, 1753 (1949).

(5) W. R. Boon and T. Leigh, *J. Chem. Soc.*, 1497 (1951).

(6) D. P. Tschudy and A. Collins, *J. Org. Chem.*, **24**, 556 (1959).

(7) F. Klaus and O. Baudisch, *Ber.*, **51**, 1044 (1918).