3,3,20,20-Bis(ethylenedioxy)-11α-(2-methoxyphenyl)-5β-pregnan-11β-ol.—2-Methoxyphenyllithium was prepared by the procedure of Gilman, *et al.*,[6] from 60 g. of 1-bromo-2-methoxybenzene and 200 ml. of 1.2 *M* ethereal butyllithium. To the aryllithium solution at 5° was added, over the course of 1 hr., a solution of 20.9 g. of 3,3,20,20-bis(ethylenedioxy)-5β-pregnan-11-one in 50 ml. of benzene and 150 ml. of ether. The mixture was stirred at room temperature overnight, and then washed several times with water, filtered through sodium sulfate, and evaporated to dryness. The crude material was dissolved in Skellysolve B and chromatographed over Florisil, from which the bulk of the material and all of the steroidal material was found in the 10% acetone–Skellysolve B eluate fractions. These were individually subjected to fractional crystallization from acetone–Skellysolve B to give 1.51 g. of 3,3,20,20-bis(ethylenedioxy)-11α-(2-methoxyphenyl)-5β-pregnan-11β-ol, m.p. 195–205°. The analytical sample was recrystallized from acetone–Skellysolve B: m.p. 203–206°; $[\alpha]^{20}\text{D}$ +84° (*c* 1, acetone); $\lambda_{\max}^{\text{EtOH}}$ 219 mμ (A_m 7225), 272 (1975), 279 (1900).

Anal. Calcd. for $C_{32}H_{46}O_6$: C, 72.97; H, 8.80. Found: C, 72.66; H, 9.40.

Hydrolysis of a 1.02-g.s ample of crude (m.p. 195–205°) 3,3,20,20-bis(ethylenedioxy)-11α-(2-methoxyphenyl)-5β-pregnan-11β-ol in 200 ml. of methanol containing 25 ml. of 1 *N* hydrochloric acid at room temperature overnight gave 0.91 g. of silky matted needles of **11β-hydroxy-11-(2-methoxyphenyl)-5β-pregnane-3,20-dione**, m.p. 191–201°. Recrystallization from acetone–Skellysolve B gave an analytical sample: m.p. 197–203°; $[\alpha]^{20}\text{D}$ +135° (*c* 1, acetone); $\lambda_{\max}^{\text{EtOH}}$ 271 mμ (A_m 1980), 278 (1920).

Anal. Calcd. for $C_{28}H_{38}O_4$: C, 76.67; H, 8.73. Found: C, 76.24; H, 8.73.

3,3,20,20-Bis(ethylenedioxy)-11α-(2-pyridylmethyl)-5β-pregnan-11β-ol.—The reaction between α-picolyllithium, prepared by the *Organic Syntheses*[7] procedure from 6.9 g. of lithium wire, and a solution of 20.9 g. of 3,3,20,20-bis(ethylenedioxy)-5β-pregnan-11-one in 100 ml. of benzene and 100 ml. of ether was carried out essentially as described for the pyridyllithium reaction. The crude product was eluted from a Florisil chromatogram by 25% acetone–Skellysolve B and was crystallized from methanol to give 13.44 g. of 3,3,20,20-bis(ethylenedioxy)-11α-(2-pyridylmethyl)-5β-pregnan-11β-ol, m.p. 148–152°. The analytical sample, recrystallized from methanol, had m.p. 154–156°, $[\alpha]^{20}\text{D}$ −58° (*c* 0.8, acetone), $\lambda_{\max}^{\text{EtOH}}$ 264 mμ (A_m 3775).

Anal. Calcd. for $C_{31}H_{45}NO_5$: C, 72.76; H, 8.86; N, 2.74. Found: C, 73.08; H, 9.32; N, 3.14.

Hydrolysis of 5.0 g. of 3,3,20,20-bis(ethylenedioxy)-11α-(2-pyridylmethyl)-5β-pregnan-11β-ol in 500 ml. of methanol containing 100 ml. of 1 *N* hydrochloric acid at room temperature overnight gave, after recrystallization from aqueous methanol, 2.68 g. of **11β-hydroxy-11α-(2-pyridylmethyl)-5β-pregnane-3,20-dione**, m.p. 167–172°. An analytical sample, m.p. 170–173°, was obtained after two recrystallizations from aqueous methanol: $[\alpha]^{20}\text{D}$ −10° (*c* 1, acetone), $\lambda_{\max}^{\text{EtOH}}$ 263 mμ (A_m 3875).

Anal. Calcd. for $C_{27}H_{37}NO_3$: C, 76.56; H, 8.81; N, 3.31. Found: C, 76.37; H, 9.06; N, 3.39.

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[6] H. Gilman, J. L. Towle, and S. M. Spatz, *J. Am. Chem. Soc.*, **68**, 2017 (1946).

[7] L. A. Walter, *Org. Syn.*, **23**, 83 (1943).

Reaction of Triphenylsilyllithium with *p*-Toluenesulfonates

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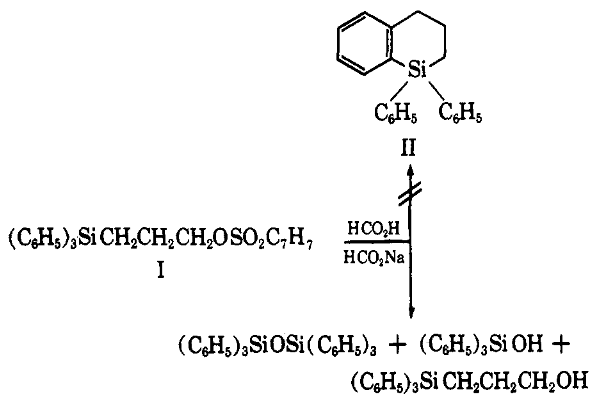
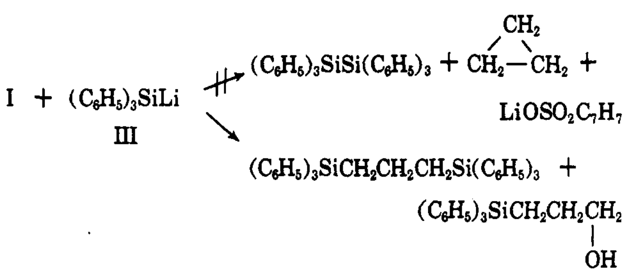
In an attempt to prepare 2:3-benzo-1,1-diphenyl-1-silacyclohex-2-ene (II)[1] by a method Heck and Winstein[2] found applicable for the preparation of tetralin, 3-triphenylsilylpropyl *p*-toluenesulfonate (I) was prepared and subjected to formolysis. However, none of II could be isolated; hexaphenyldisiloxane, triphenylsilanol, and 3-triphenylsilylpropanol-1 were the major products. A trace of a solid melting at 81–82° was also obtained, but this was not II, allyl- or propenyltriphenylsilane. Since hexaphenyldisiloxane and triphenylsilanol are probably products of γ-elimination, it was postulated that triphenylsilyllithium (III) would react with I to give the highly insoluble hexaphenyldisilane *via* γ-elimination, a reaction previously observed between 3-bromopropyltrimethylsilane and aluminum chloride,[3] 3-bromopropyltrichlorosilane and base,[3] and heating 3-chloropropyldiethylmethylsilane.[4]





However, in only one of three runs was hexaphenyldisilane isolated, and then in a low yield (5.6%). The preferred reaction appears to be a normal alkylation reaction as 1,3-bis(triphenylsilyl)propane[5] was obtained. When a 1:1 ratio of the silyllithium to the sulfonate was employed, a 41.6% yield of 3-triphenylsilylpropanol-1 was isolated along with the propane (34%). When 2 equiv. of III were added to 1 equiv. of the sulfonate I, the yield of the propanol was 9.4% and that of the propane was 53.5%. Other products were triphenylsilane (9.6%), tetraphenylsilane (2.5%), and triphenylsilanol (5.1%). The fact that 2 equiv. of III were required to give good yields of the propane derivative (almost 2 equiv. of VI were added before Color Test I[7] became positive) was surprising, as III

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[1] See, H. Gilman and O. L. Marrs [*J. Org. Chem.*, **29**, 3175 (1964); **30**, 1942 (1965)] for the synthesis and properties of these compounds.

[2] R. Heck and S. Winstein, *J. Am. Chem. Soc.*, **79**, 3105 (1957).

[3] L. H. Sommer, R. E. Van Strien, and F. C. Whitmore, *ibid.*, **71**, 3056 (1949).

[4] V. A. Ponomarenko, B. A. Sokolov, Kh. M. Minachev, and A. D. Petrov, *Proc. Acad. Sci. USSR, Chem. Sect.* (Eng. Transl.), **106**, 17 (1956).

[5] This compound has been reported [N. S. Nametkin, A. V. Topchiev, T. I. Chernusheva, and S. D. Durgar'yan, *Tr. Mosk. Neft. Inst.*, **22**, (1958); *Chem. Abstr.*, **53**, 18894 (1959)] to melt at 209.5–210°, but the compound has also been prepared from triphenylsilyllithium and 3-bromopropyltriphenylsilane and has been found to melt at 131–132°.

[6] H. Gilman, D. Aoki, and D. Wittenberg, *J. Am. Chem. Soc.*, **81**, 1107 (1959).

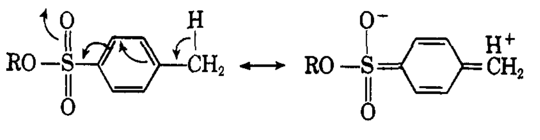
[7] H. Gilman and F. Schulze, *ibid.*, **47**, 2002 (1925).

has been observed[8] to react smoothly with alkyl phosphates in 1:1 mole ratios to give excellent yields (88–98%) of the alkylation products. If the alkylation reaction is to occur with sulfonates, one would expect similar yields, but the isolation of tetraphenylsilane suggested that triphenylsilane was being formed and was reacting with the silyllithium reagent to give tetraphenylsilane.[9] This would explain the necessity of more than 1 equiv. of the silyllithium compound per equivalent of the *p*-toluenesulfonate. To test the possibility that triphenylsilane was being formed during the reaction (triphenylsilane and III would give tetraphenylsilane if the reaction mixture is allowed to stir overnight), III was allowed to react with I in a 2:1 molar ratio and the mixture was carbonated. The products were triphenylsilane (23.8%), 1,3-bis(triphenylsilyl)propane (58.4%), and triphenylsilanol (4.8%).

$$\mathrm{I} + 2\mathrm{III} \xrightarrow{CO_2} (C_6H_5)_3SiH + (C_6H_5)_3SiCH_2CH_2CH_2Si(C_6H_5)_3 + (C_6H_5)_3SiOH$$

The triphenylsilane must have been formed prior to carbonation as it has been shown that carbonation of III[10a] gives only the acid and some of the decarbonylation products.[10b,c] Similar results were obtained with *n*-butyl *p*-toluenesulfonate and the silyllithium reagent III. When the reaction mixture was allowed to stir overnight and then hydrolyzed, tetraphenylsilane (1.5%) and the alkylation product, *n*-butyltriphenylsilane (71.1%), were isolated. In a repeat run, chlorotriphenylsilane was added to the reaction mixture to remove any unreacted III. Among the products was triphenylsilane, which must have been formed prior to hydrolysis.

The triphenylsilane could arise by removal of a proton from the aliphatic chain β to the sulfonate grouping, followed by β-elimination, although the olefin could not be isolated, or it may arise by lateral metalation of the tolyl group. The metalating ability of III has been studied[11] and this compound has been found to metalate toluene to a limited extent. The presence of the sulfonyl group may enhance lateral metalation of the tolyl group owing to electron withdrawal. *ortho* metalation of diphenylsulfone with *n*-butyllithium is well known,[12] but triphenylsilyllithium or -potassium has been reported not to metalate the sulfone.[13]



Experimental[14]

3-Triphenylsilylpropyl *p*-Toluenesulfonate.—The sulfonate was prepared according to a published procedure[15] from 48.56 g. (0.151 mole) of 3-triphenylsilylpropanol-1[16] and 32.4 g. (0.17 mole) of *p*-toluenesulfonyl chloride in 80 ml. of pyridine. The crude product was recrystallized from petroleum ether (b.p. 60–70°) to give 60.9 g. (85.4%) of colorless crystals, m.p. 102–104.5°. A portion was recrystallized from absolute ethanol to afford an analytical sample melting at 103–104.5°.

Anal. Calcd. for $C_{28}H_{28}O_3SSi$: Si, 5.94. Found: Si, 5.80, 5.87.

Formolysis of 3-Triphenylsilylpropyl *p*-Toluenesulfonate.—A mixture of the sulfonate (30 g., 0.063 mole) and previously dried sodium formate (5.15 g., 0.076 mole) in 500 ml. of dry formic acid[17] was stirred 10 hr. at room temperature and 48 hr. at 70°. The clear solution was poured into an excess of water and extracted with ether. The ether extracts were combined, washed neutral with sodium bicarbonate, and dried. The solvent was distilled and the residue was chromatographed on alumina.

Elution with petroleum ether gave 0.04 g. of a solid which melted at 81–82° after recrystallization from ethanol. Mixture melting point determinations with authentic samples of 2:3-benzo-1,1-diphenyl-1-silacyclohex-2-ene, allyltriphenylsilane, and propenyltriphenylsilane were depressed. Continued elution with cyclohexane gave 2.04 g. (12.1%) of a solid, m.p. 227–229°, identified as hexphenyldisiloxane by mixture melting point and by comparison of the infrared spectra. Benzene elution afforded 11.7 g. (57.9%) of 3-triphenylsilylpropanol-1, m.p. and m.m.p. 137–139°. Final elution of the column with methanol gave 0.2 g. of triphenylsilanol, m.p. and m.m.p. 149–150°.

Reaction of Triphenylsilyllithium with 3-Triphenylsilylpropyl *p*-Toluenesulfonate. A. 1:1 Ratio.—Triphenylsilyllithium (0.015 mole), prepared by the lithium cleavage of 3.89 g. (0.0075 mole) of hexaphenyldisilane in 50 ml. of tetrahydrofuran (THF)[18] was added to 7.09 g. (0.015 mole) of 3-triphenylsilylpropyl *p*-toluenesulfonate dissolved in 12 ml. of THF. Heat was evolved and the solution became turbid. Color Test I was negative subsequent to complete addition. The mixture was hydrolyzed and the aqueous layer was extracted thoroughly with ether. The extracts were dried and the solvents were evaporated. The residual material was treated with petroleum ether to give 0.22 g. (5.6%) of hexaphenyldisilane, m.p. and m.m.p. 356–359°.

The filtrate was chromatographed over alumina. Elution with petroleum ether and cyclohexane gave 3.44 g. of a colorless solid, m.p. 125–195°. Recrystallization from petroleum ether afforded 2.86 g. (34%) of 1,3-bis(triphenylsilyl)propane, m.p. 131–132°. A mixture melting point with an authentic sample[6] was not depressed. A small amount of oil was eluted with benzene, and final elution with methanol gave 2.69 g. of solid melting over the range 122–132°. Recrystallization from a benzene–petroleum ether mixture afforded 2.0 g. (41.6%) of 3-triphenylsilylpropanol-1, m.p. 135–137°, identified by mixture melting point.

B. 2:1 Ratio.—A tetrahydrofuran (THF) solution containing 0.023 mole of triphenylsilyllithium was added to 7.09 g. (0.015 mole) of 3-triphenylsilylpropyl *p*-toluenesulfonate dissolved in THF. Color Test I was negative. An additional 0.007 mole of the silyllithium reagent was added and the mixture was stirred 18 hr. at room temperature. After acid hydrolysis and the usual work-up, the concentrated organic layer was treated with petroleum ether, but hexaphenyldisilane could not be detected. Chromatography of the reaction products gave 0.75 g. (9.6%) of triphenylsilane, m.p. 45–47° (with petroleum ether); 0.25 g. (2.5%) of tetraphenylsilane, m.p. 225–228° (also with petroleum ether); 4.5 g. (53.5%) of 1,3-bis(triphenylsilyl)propane, m.p. 131–132° (with cyclohexane); 0.45 g. (9.4%) of 3-triphenylsilylpropanol-1, m.p. 133–135° (with ethyl acetate); and 0.42 g. (5.1%) of triphenylsilanol, m.p. 150–152° (with methanol). All compounds were identified by mixture melting points with authentic samples and by comparison of the infrared spectra.

In a repeat run, 0.03 mole of triphenylsilyllithium was added to 7.09 g. (0.015 mole) of the *p*-toluenesulfonate dissolved in 20 ml. of tetrahydrofuran. When the addition was complete, the mixture was carbonated by pouring onto a Dry Ice–ether slurry.

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[8] H. Gilman and B. J. Gaj, *J. Org. Chem.*, **26**, 2471 (1961).

[9] For an account of the mechanism of the formation of tetraphenylsilane from triphenylsilane and triphenylsilyllithium, see H. Gilman and D. J. Peterson, *ibid.*, in press.

[10] (a) M. V. George and H. Gilman, *J. Am. Chem. Soc.*, **81**, 3288 (1959); (b) R. A. Benkesdder and R. G. Severson, *ibid.*, **73**, 1424 (1951); (c) A. G. Brook and H. Gilman, *ibid.*, **77**, 2322 (1955).

[11] H. Gilman, O. L. Marrs, W. J. Trepka, and J. W. Diehl, *J. Org. Chem.*, **27**, 1260 (1962).

[12] (a) W. E. Truce and M. F. Amos, *J. Am. Chem. Soc.*, **73**, 3013 (1951); (b) H. Gilman and D. L. Esmay, *ibid.*, **75**, 278 (1953).

[13] D. Wittenberg, T. C. Wu, and H. Gilman, *J. Org. Chem.*, **23**, 1898 (1958).

[14] All melting and boiling points are uncorrected. Reactions involving organometallic reagents were conducted under an atmosphere of dry, oxygen-free nitrogen. All solvents were pure and anhydrous.

[15] A. I. Vogel, "Practical Organic Chemistry," 3rd Ed., Longmans, Green and Co., Inc., New York, N. Y., 1959, p. 825.

[16] D. Wittenberg, D. Aoki, and H. Gilman, *J. Am. Chem. Soc.*, **80**, 5933 (1958).

[17] S. Winstein and H. Marshall, *ibid.*, **74**, 1120 (1952).

[18] H. Gilman and G. D. Lichtenwalter, *ibid.*, **80**, 608 (1958).

The mixture was hydrolyzed and worked up in the usual manner. The concentrated organic layer was chromatographed on alumina. The petroleum ether eluates gave 7.1 g. of crude 1,3-bis-(triphenylsilyl)propane, m.p. 116–122°. Recrystallization from the same solvent raised the melting point to 131–132° and afforded 4.9 g. (58.4%) of pure product. Concentration of the petroleum ether filtrates gave 1.86 g. (23.8%) of triphenylsilane, identified by comparison of the infrared spectra. From the ethyl acetate eluates, there was obtained 0.4 g. (4.8%) of triphenylsilanol, m.p. and m.m.p. 151–153°.

Reaction of Triphenylsilyllithium with *n*-Butyl *p*-Toluenesulfonate.—To a solution of *n*-butyl *p*-toluenesulfonate (10.96 g., 0.048 mole) in 50 ml. of tetrahydrofuran (THF) was added 0.096 mole of triphenylsilyllithium in 200 ml. of THF. When the addition was complete, Color Test I was indefinite; the green color of the color test developed very slowly and then only with a large excess of iodine. The mixture was stirred overnight and hydrolyzed. After the usual separation, extraction and drying techniques, the concentrated oil was chromatographed on a column of alumina. Elution with petroleum ether gave 12.04 g. of impure *n*-butyltriphenylsilane, m.p. 82–86°. After recrystallization from ethanol, 10.8 g. (71.1%) of pure product was obtained, m.p. and m.m.p. 85–86.5°.

The ethanol-insoluble material (1.04 g.) was recrystallized from a benzene–petroleum ether mixture to give 0.48 g. (1.5%) of tetraphenylsilane, m.p. and m.m.p. 232–234°. Also, the infrared spectra were superimposable.

The reaction was repeated using the silyllithium reagent and sulfonate. After stirring 30 min. at room temperature, chlorotriphenylsilane (3 g., 0.01 mole) was added and then the mixture was carbonated. Addition of petroleum ether to the concentrated organic layer gave 0.14 g. (0.28%) of hexaphenyldisilane. Chromatography of the filtrate gave 8.35 g. (55%) of *n*-butyltriphenylsilane, m.p. 84–86°. Concentration of the mother liquor afforded 1.12 g. of a mixture of triphenylsilane and *n*-butyltriphenylsilane as determined by infrared analysis. Elution with benzene and ethanol gave 3.53 g. (22%) of triphenylsilanol, m.p. and m.m.p. 149–151°.

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Structure of Cyclization Products of Substituted 2-Amino-N-(2-hydroxyethyl)benzamides

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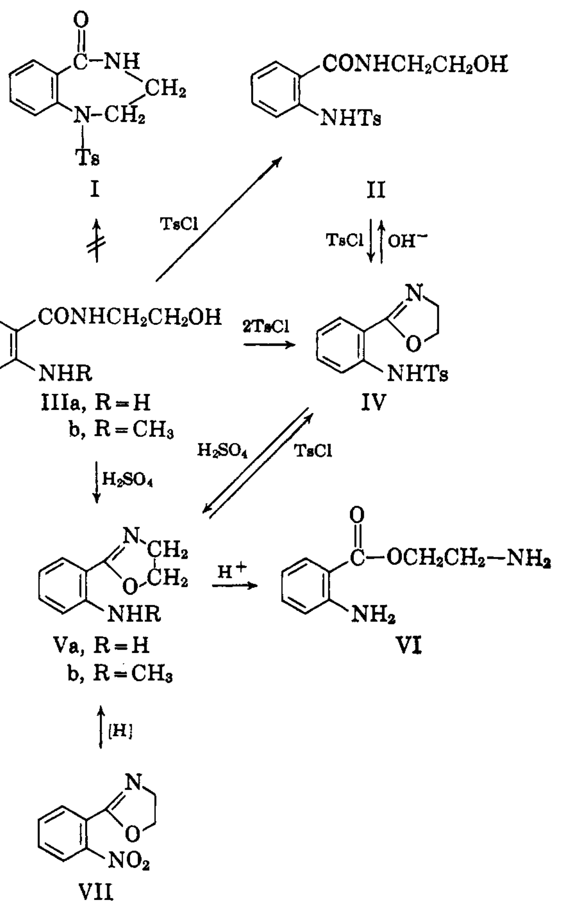
In view of our experience in the 1,4-benzodiazepine field[1] we were highly interested in a recently published new method for the synthesis of compounds of this type and related heterocyclic products.[2] This method consists in the cyclization of substituted 2-amino-N-(2-hydroxyethyl)benzamides with dehydrating agents. For example, treatment of the hydroxyethylamide IIIa with *p*-toluenesulfonyl chloride was reported to yield the benzodiazepine I (Scheme I).

SCHEME I



We sought to extend this method to the synthesis of an analog of I in which the tosyl group was replaced by a methyl group. Thus, we treated the N-methyl derivative IIIb with thionyl chloride and obtained a product of the expected elemental composition. This compound showed an infrared absorption band at 1639 cm.$^{-1}$ (6.1 μ) as did the products described by Santilli and Osdene[2a]; however, closer investigation indicated that it could not be the postulated benzodiazepine. The n.m.r. spectrum shows a doublet at δ = 2.9 p.p.m. due to the N-methyl group, which collapses to a singlet on exchange with deuterium oxide. This shows that the proton attached to the nitrogen of the methylamino group is still intact and that the reaction has taken an alternative course to form the oxazoline derivative Vb. Indeed, Cornforth[3] cites several examples of the synthesis of oxazolines by similar methods.

In order to establish whether or not the presence of an N-methyl group had affected the course of the cyclization reaction we repeated the reactions which were reported by Santilli and Osdene[2a,f] to give the benzodiazepine I. We obtained a product possessing the physical properties reported by them, but found that this compound was not a 1,4-benzodiazepine derivative, but rather the 2-aminophenyloxazoline derivative IV.

The structure was established by comparison of the detosylated product Va, obtained by treatment of IV with concentrated sulfuric acid,[2a] with an authentic sample of 2-(*o*-aminophenyl)-2-oxazoline prepared by catalytic reduction of the nitrophenyloxazoline VII described by Leffler and Adams.[4] Leffler and Adams

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[1] Paper XXIV: W. Metlesics, R. F. Tavares, and L. H. Sternbach, *J. Org. Chem.*, **30**, 1311 (1965), and previous papers in this series; see also M. Uskoković, J. Iacobelli, and W. Wenner, *ibid.*, **27**, 3606 (1962).

[2] (a) A. Santilli and T. S. Osdene, *ibid.*, **29**, 1998 (1964); (b) *ibid.*, **29**, 2066 (1964).

[3] J. W. Cornforth, "Heterocyclic Compounds," Vol. 5, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1957, p. 378.

[4] M. T. Leffler and R. Adams, *J. Am. Chem. Soc.*, **59**, 2252 (1937).