The Synthesis of Certain N,N'-Di-(*p*-carbomethoxyalkylphenyl)-polymethylenediamines

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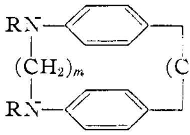
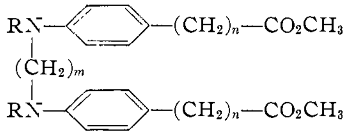
RECEIVED OCTOBER 31, 1953

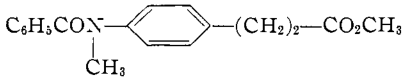
As a part of a research program on heterocyclic compounds containing two *p*-phenylene units[2] it was planned to prepare compounds of type I by way of the acyloin ring closure. This paper reports the synthesis of five esters (II–VI) designed for cyclization by this method. Attempts at ring closure, however, have yielded only polymeric products. Failure with the benzoyl compounds (II, III) may be due to attack of the amide groups. In fact, a model compound VII of this type likewise failed to undergo the acyloin condensation.



I

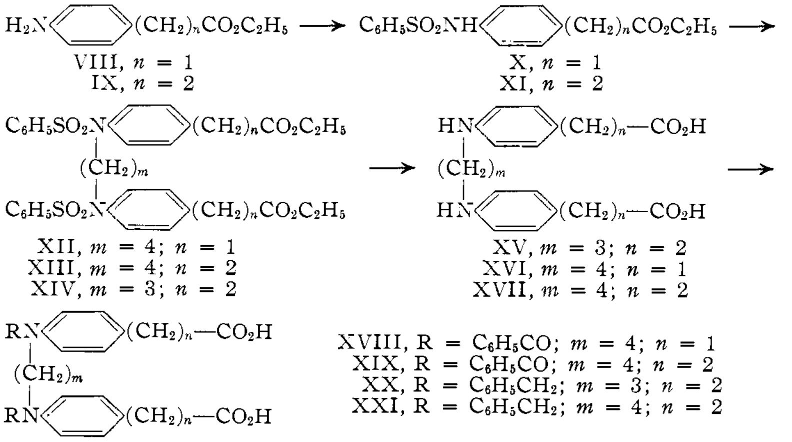


II, R = C_6H_5CO; $m = 4$; $n = 1$
III, R = C_6H_5CO; $m = 4$; $n = 2$
IV, R = H; $m = 4$; $n = 2$
V, R = $C_6H_5CH_2$; $m = 4$; $n = 2$
VI, R = $C_6H_5CH_2$; $m = 3$; $n = 2$



VII

The following outline shows the synthetic route used to make the acids corresponding to the esters of the free diamine IV, the benzamides II, III and the benzyl derivatives V, VI.



VIII, $n = 1$
IX, $n = 2$
X, $n = 1$
XI, $n = 2$
XII, $m = 4$; $n = 1$
XIII, $m = 4$; $n = 2$
XIV, $m = 3$; $n = 2$
XV, $m = 3$; $n = 2$
XVI, $m = 4$; $n = 1$
XVII, $m = 4$; $n = 2$
XVIII, R = C_6H_5CO; $m = 4$; $n = 1$
XIX, R = C_6H_5CO; $m = 4$; $n = 2$
XX, R = $C_6H_5CH_2$; $m = 3$; $n = 2$
XXI, R = $C_6H_5CH_2$; $m = 4$; $n = 2$

Experimental[3]

Ethyl *p*-Benzenesulfonamidophenylacetate (X).—The reduction of 70 g. of ethyl *p*-nitrophenylacetate, initiated at a pressure of 1700 lb. per sq. in and carried out at room temperature in ethanol solution and in the presence of Raney nickel,[4] gave 57 g. of ethyl *p*-aminophenylacetate (VIII). The crude amine was dissolved in 200 ml. of pyridine and 80 ml. of benzenesulfonyl chloride was added. The solution was heated for 80 minutes on a steam-bath and poured on ice. The amido ester crystallized from dilute ethanol in colorless needles; m.p. 95–96°, yield 91 g. The analytical sample, prepared by recrystallization from dilute ethanol, melted at 96.5–97.5°.

Anal.[5] Calcd. for $C_{16}H_{17}NO_4S$: C, 60.17; H, 5.37; N, 4.39. Found: C, 60.21; H, 5.57; N, 4.20.

N,N'-Dibenzenesulfonyl-N,N'-di-(*p*-carbethoxymethylphenyl)-tetramethylenediamine (XII).—A mixture of 30 g. of ethyl *p*-benzenesulfonamidophenylacetate, 10.5 g. of tetramethylene bromide, 100 ml. of acetone and 30 g. of powdered anhydrous potassium carbonate was heated under reflux, with efficient stirring, for 5 hours and poured on 300 g. of ice. The product was washed with ethanol and ether and recrystallized from ethanol; m.p. 125–126°, yield 68%. After repeated recrystallization from 95% ethanol, it formed colorless crystals melting at 126–127°.

Anal. Calcd. for $C_{36}H_{40}O_8S_2$: C, 62.41; H, 5.82; N, 4.04. Found: C, 62.45; H, 5.91; N, 4.12.

N,N'-Di-(*p*-carboxymethylphenyl)-tetramethylenediamine (XVI).—A mixture of 21 g. of the dibenzenesulfonamide (XII), 40 g. of phenol and 200 ml. of 48% hydrobromic acid was heated under reflux, with efficient stirring, for 4 hours, allowed to cool and diluted with 100 ml. of ether. The dihydrochloride of the amine was washed with ether and dissolved in 200 ml. of boiling water; and to the solution, after filtration, was added enough potassium or sodium acetate to precipitate the diamine XVI completely; m.p. 176–178° dec., yield 84%. Recrystallization of the product from 95% ethanol did not change the melting point.

Anal. Calcd. for $C_{20}H_{24}N_2O_4$: C, 67.39; H, 6.79; N, 7.86. Found: C, 67.22; H, 6.94; N, 7.91.

N,N'-Dibenzoyl-N,N'-di-(*p*-carbomethoxymethylphenyl)-tetramethylenediamine (II).—A solution of 9.0 g. of the diamine XVI in 55 ml. of 2 *N* aqueous sodium hydroxide was shaken for 5 minutes with 7.4 g. of benzoyl chloride. The resulting solution was extracted with ether and acidified with acetic acid to precipitate the dibenzoyl compound XVIII; m.p. 245–247°, yield 86%. It is only slightly soluble in common solvents. The analytical sample, prepared by treating the substance twice with boiling methanol, was a white powder; m.p. 254–256°.

Anal. Calcd. for $C_{34}H_{32}N_2O_6$: C, 72.32; H, 5.71; N, 4.96. Found: C, 72.12; H, 5.62; N, 4.99.

Esterification was accomplished by dissolving 5 g. of the acid XVIII in 50 ml. of methanol, previously saturated with dry hydrogen chloride, and allowing the solution to stand for 5 hours at room temperature. After 400 ml. of ether had been added, the solution was washed with aqueous sodium hydroxide and with water and dried over sodium sulfate. The ether was distilled on a steam-bath and the residue, after being allowed to stand at room temperature to allow the remaining traces of solvent to evaporate, weighed 4.1 g. (79%); m.p. 93–95°. The ester II was purified by recrystallization from ether; m.p. 98–99°.

Anal. Calcd. for $C_{36}H_{36}N_2O_6$: C, 72.95; H, 6.12; N, 4.72. Found: C, 72.68; H, 6.28; N, 4.97.

Ethyl *p*-Benzenesulfamidophenylpropionate (XI).—Ethyl *p*-aminophenylpropionate was obtained in nearly theoretical yield by catalytic hydrogenation of ethyl *p*-nitrocinnamate in ethanol over Raney nickel at room temperature and at an initial pressure of 1700 lb. per sq. in. The crude amine was transformed directly into the benzenesulfonamide by the method already described for the lower homolog X. The amide was recrystallized from dilute ethanol; m.p. 82–84°, yield 89% (based on nitro ester). The analytical sample was prepared by recrystallization from dilute ethanol; m.p. 84–85°.

Anal. Calcd. for $C_{17}H_{19}NO_4S$: C, 61.24; H, 5.74; N, 4.20. Found: C, 61.31; H, 5.99; N, 4.19.

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[1] Fellow of the "Stiftung für Stipendien auf dem Gebiete der Chemie (Switzerland)."

[2] R. C. Fuson and H. O. House, THIS JOURNAL, **75**, 1325, 1327, 5744 (1953).

[3] All melting points are corrected.

[4] The catalytic reduction had previously been carried out only in the presence of platinum (E. Ferber and H. Bendix, *Ber.*, **72B**, 841 (1939)].

[5] The microanalyses are by Mrs. K. Pih, Miss L. Chang, Mrs. E. Fett and Mr. J. Nemeth.

N,N′-Dibenzenesulfonyl-N,N′-di-(*p*-carbethoxyethylphenyl)-tetramethylenediamine (XIII).—A mixture of 30 g. of the amide XI, 100 ml. of acetone, 10.5 g. of tetramethylene bromide and 30 g. of powdered anhydrous potassium carbonate was heated under reflux, with efficient stirring, for 12 hours and poured on ice. The product, after trituration with ether, was a white powder; m.p. 109–111°, yield 83%. It was purified by recrystallization from methanol; m.p. 110.5–111.5°.

Anal. Calcd. for $C_{38}H_{44}N_2O_8S_2$: C, 63.31; H, 6.15; N, 3.89. Found: C, 63.50; H, 6.54; N, 3.84.

N,N′-Di-(*p*-carboxyethylphenyl)-tetramethylenediamine (XVII).—This compound was prepared from the ester XIII by the method for the preparation of the lower homolog XVI; yield 88%. The product, purified for analysis by recrystallization from 95% ethanol, was a colorless crystalline powder; m.p. 182–184° dec.

Anal. Calcd. for $C_{22}H_{28}N_2O_4$: C, 68.72; H, 7.34; N, 7.29. Found: C, 68.98; H, 7.40; N, 7.36.

N,N′-Dibenzoyl-N,N′-di-(*p*-carboxyethylphenyl)-tetramethylenediamine (XIX).—A mixture of 13.9 g. of the diamine XVII, 11.5 g. of benzoyl chloride and 80 ml. of 2 *N* sodium hydroxide was shaken for 2 hours at room temperature and acidified with acetic acid. The product was a gum which crystallized from dilute ethanol; m.p. 186–189°, yield 79%. Further recrystallization from dilute ethanol gave colorless leaflets; m.p. 192.5–194° dec.

Anal. Calcd. for $C_{36}H_{36}N_2O_6$: C, 72.95; H, 6.12; N, 4.73. Found: C, 72.95; H, 6.00; N, 4.84.

In contrast to its homolog XVIII, this compound is remarkably soluble in methanol and in ethanol. Its melting point is also much lower.

N,N′-Dibenzoyl-N,N′-di-(*p*-carbomethoxyethylphenyl)-tetramethylenediamine (III).—The method described for the lower homolog II was followed. The crude product melted at 106–107°; yield 75%. It was purified by recrystallization from ether; m.p. 107–108°.

Anal. Calcd. for $C_{38}H_{40}N_2O_6$: C, 73.53; H, 6.50; N, 4.51. Found: C, 73.85; H, 6.75; N, 4.69.

Methyl *p*-Benzaminophenylpropionate.—A solution of 22 g. of crude ethyl *p*-aminophenylpropionate, prepared as described earlier in 50 ml. of pyridine was treated with 32 g. of benzoyl chloride at room temperature for two hours and poured on ice. The benzoylated ester, isolated by usual procedures, was dissolved in 100 ml. of 95% ethanol and to the solution was added 40 ml. of a 20% sodium hydroxide solution. After the mixture had been heated under reflux for 10 minutes, with stirring, it was cooled in an ice-bath. The sodium *p*-benzaminophenylpropionate was washed with ethanol and ether and dissolved in boiling water. After filtration the hot solution was acidified with dilute hydrochloric acid. The yield of *p*-benzaminophenylpropionic acid was 20 g.; m.p. 192–193°. The amido acid was purified by recrystallization from dilute acetic acid; it formed leaflets melting at 195–196°. The melting point reported by Heller is 194–195°.[6]

A current of dry hydrogen chloride was passed into a solution of the acid in 100 ml. of absolute methanol. After being allowed to stand 5 hours at room temperature, the mixture was poured on ice and the product isolated in the usual way; m.p. 111–112°, yield 78%. The methyl ester was recrystallized from methanol; m.p. 112.5–113°.

Anal. Calcd. for $C_{17}H_{17}NO_3$: C, 72.06; H, 6.05; N, 4.95. Found: C, 72.06; H, 6.13; N, 4.88.

Methyl N-Benzoyl-*p*-Methylaminophenylpropionate (VII). The method was patterned after that of Pachter and Kloetzel.[7] A mixture of 10 g. of potassium hydroxide, finely powdered under acetone, 100 ml. of acetone and 22.8 g. of methyl iodide was heated to gentle boiling and a solution of 10 g. of methyl *p*-benzaminophenylpropionate in 50 ml. of acetone was added over a 10-minute period. Heating under reflux, with stirring, was continued for 3 hours. After filtration of the mixture the solution was concentrated on a steam-bath to about 20 ml. and then diluted with 100 ml. of ether to complete the precipitation of the potassium iodide. After a second filtration the solvent was removed on a steam-bath. The residue was induced to crystallize by treatment with low-boiling petroleum ether and cooling in an acetone–solid carbon dioxide bath; 58–59°, yield 90%. The ester was purified by recrystallization from a mixture of ether and low-boiling petroleum ether. It formed colorless leaflets; m.p. 59–60°.

Anal. Calcd. for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.98; H, 6.16; N, 4.70.

N-Benzoyl-*p*-methylaminophenylpropionic Acid.—A solution of 2 g. of the methyl ester, 10 ml. of 95% ethanol, 0.5 g. of sodium hydroxide and 3 ml. of water was boiled for one minute, cooled, diluted with water and acidified with hydrochloric acid; m.p. 121–122°, yield 94%. A recrystallization from dilute ethanol gave colorless needles melting at the same temperature.

Anal. Calcd. for $C_{17}H_{17}NO_3$: C, 72.06; H, 6.05; N, 4.95. Found: C, 71.94; H, 6.26; N, 5.11.

N,N′-Di-(*p*-carbomethoxyethylphenyl)-tetramethylenediamine (IV).—A current of hydrogen chloride was passed into a solution of 7 g. of the amino acid XVII in 70 ml. of absolute methanol. The mixture was allowed to cool and was diluted with 70 ml. of ether. The hydrochloride of the amino ester was washed with ether and dissolved in 300 ml. of boiling water. The solution was allowed to cool somewhat and was then carefully neutralized with dilute ammonium hydroxide. When the mixture had become cold a slight excess of ammonium hydroxide was added. The yield of product was 88%; m.p. 119–120°. The analytical sample was recrystallized from methanol; m.p. 119.5–120°.

Anal. Calcd. for $C_{24}H_{32}N_2O_4$: C, 69.87; H, 7.82; N, 6.79. Found: C, 69.39; H, 7.86; N, 6.83.

N,N′-Dibenzyl-N,N′-di-(*p*-carbomethoxyethylphenyl)-tetramethylenediamine (V).—To a solution of 8 g. of the dicarboxylic acid XVII, 2.5 g. of sodium carbonate and 40 ml. of water was added a solution of 6.2 g. of benzyl chloride in 80 ml. of acetone. The mixture was heated under reflux, with stirring, for 90 minutes and concentrated on a steam-bath. A solution of the residue in dilute ammonium hydroxide was extracted with ether and acidified with cold acetic acid. The product separated as an oil which soon crystallized; it was recrystallized from dilute ethanol; m.p. 138–142° dec., yield 81%. Further recrystallization of the compound from dilute ethanol did not change the melting point.

Anal. Calcd. for $C_{36}H_{40}N_2O_4$: C, 76.57; H, 7.14; N, 4.96. Found: C, 76.62; H, 7.26; N, 4.98.

The acid XXI was converted to the methyl ester by treatment with absolute methanol (100 ml.) saturated with hydrogen chloride; m.p. 103.5–105°, yield 95%. The ester, purified by recrystallization from methanol, formed colorless leaflets; m.p. 106–107°.

Anal. Calcd. for $C_{38}H_{44}N_2O_4$: C, 76.99; H, 7.48; N, 4.73. Found: C, 76.70; H, 7.48; N, 4.75.

This ester was also prepared by benzylation of the amine IV but the method was less satisfactory.

N,N′-Dibenzyl-N,N′-di-(*p*-carbomethoxyethylphenyl)-trimethylenediamine (VI).—N,N′-Dibenzenesulfonyl-N,N′-di-(*p*-carbethoxyethylphenyl)-trimethylenediamine (XIV) was prepared from ethyl *p*-benzenesulfonamidophenylpropionate (XI) by a procedure similar to that employed for the higher homolog XIII. The product, however, was an oil which could not be induced to crystallize. It was transformed into the free acid XV by the procedure described for XVI, m.p. 145–147°, yield 70% (based on XI). The analytical sample was recrystallized from dilute ethanol; it melted at 133°, resolidified and melted a second time at 148.5–149.5°.

Anal. Calcd. for $C_{21}H_{26}N_2O_4$: C, 68.09; H, 7.08; N, 7.56. Found: C, 67.91; H, 7.29; N, 7.60.

N,N′-Dibenzyl-N,N′-di-(*p*-carboxyethylphenyl)-trimethylenediamine (XX).—A method similar to that described for XII gave the amino acid (m.p. 162–163°) in a yield of 73%. The analytical sample, crystallized from dilute ethanol, melted with decomposition at 167–169°.

Anal. Calcd. for $C_{35}H_{38}N_2O_4$: C, 76.33; H, 6.95; N, 5.09. Found: C, 76.47; H, 6.68; N, 5.07.

The acid XX was esterified according to the procedure for the higher homolog V. After one recrystallization from dilute methanol, the ester melted at 65–66°, yield 94%. The analytical sample crystallized from dilute methanol in leaflets, m.p. 67.5–68°.

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[6] G. Heller, *Ber.*, **46**, 3982 (1913).

[7] I. J. Pachter and M. C. Kloetzel, THIS JOURNAL, **74**, 1321 (1952).

Anal. Calcd. for $C_{37}H_{42}N_2O_4$: C, 76.78; H, 7.32; N, 4.84. Found: C, 76.51; H, 7.36; N, 4.94.

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The Synthesis and Polymerization of N-Phenylethylenimine and the Synthesis of N,N'-Diphenylpiperazine

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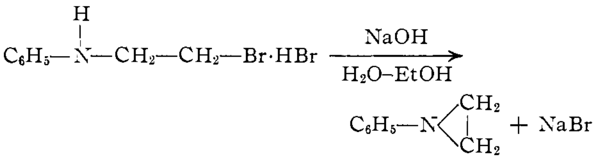
In the course of studies on the chemistry of ethylenimine we had occasion to synthesize N-phenylethylenimine. This compound was prepared from N-β-bromoethylaniline hydrobromide by a slight modification of the general method of Gabriel,[1] *e.g.*



Although N-phenylethylenimine is formed with considerable readiness and in 68% yield under these conditions the course of the reaction may be so altered that N,N'-diphenylpiperazine is formed as the main reaction product.

The structure of N-phenylethylenimine was established by elementary analysis and by its reaction with hydrobromic acid to form N-β-bromoethylaniline hydrobromide. An infrared analysis showed the absence of any N–H fundamental in the region of 2.9 μ, which is in accord with expectations.

N-Phenylethylenimine rapidly polymerized to a colorless solid when it was emulsified with water or was exposed to air. Polymerization also took place when N-phenylethylenimine was dissolved in methanol or ethanol and exposed to air but at a much slower rate than in water. Nitrogen analysis of the polymer gave a value corresponding to the monomer. Most likely a chain polymer was produced. The polymer was soluble in 90% formic acid and decomposed at 270–275°.

Experimental

N-Phenylethylenimine.—A solution of 115 ml. of 6 *N* sodium hydroxide and 300 ml. of 95% ethanol was placed in a one-liter three-necked flask equipped with a stirrer, condenser and dropping funnel, and the flask immersed in a water-bath held at 50°. To this was added dropwise and with stirring 84.3 g. of N-β-bromoethylaniline hydrobromide[2] dissolved in 120 ml. of water and 80 ml. of 95% ethanol. After the addition was completed the water-bath was raised to 85° for one hour. The condenser was then arranged for downward distillation and 220 ml. of ethanol was removed by distillation. The residue was cooled to room temperature and extracted with six 50-ml. portions of ether. The ethereal solution was dried over sodium sulfate, filtered and distilled until the temperature reached 82°. The residue separated into two layers at this point. The lower layer consisted of water and ethanol. The top layer was removed by means of a suction pipet, dried with sodium sulfate and subjected to vacuum distillation. A fraction of 24.3 g. (68%) boiling at 70–70.5° at 13 mm. or 60.5–61° at 9 mm. was obtained; n^{25}D 1.5498, n^{20}D 1.5524.

Anal. Calcd. for C_8H_9N: C, 80.5; H, 7.6; N, 11.8. Found[3]: C, 80.5; H, 7.7; N, 11.8.

The N-phenylethylenimine was converted into N-β-bromoethylaniline hydrobromide by the following procedure: 2.2 g. of N-phenylethylenimine was added quickly to 60 ml. of cold 48% hydrobromic acid. The reaction mixture was refluxed gently for one-half hour and then distilled until 50 ml. of distillate was collected. The residue was cooled in a vacuum desiccator. The crude N-β-bromoethylaniline hydrobromide crystallized on standing. Recrystallization from absolute ethanol gave a 65% yield of pure N-β-bromoethylaniline hydrobromide melting at 138–139°. A mixture of this substance with authentic N-β-bromoethylaniline hydrobromide melted at 137–140°.

Poly-N-phenylethylenimine.—Two grams of N-phenylethylenimine was shaken with 25 ml. of water. The emulsion rapidly became milky-white and a precipitate formed within an hour. This material was filtered and dried; yield 1.94 g. The polymer turned brown at 230° and gradually shriveled and melted completely at 270–275°.

Anal. Calcd. for $(C_8H_9N)_n$: N, 11.8. Found: N, 11.6.

N,N'-Diphenylpiperazine.—To 17.6 g. of N-β-bromoethylaniline hydrobromide was added a solution containing 6 g. of NaOH in 10 ml. of water. Two layers formed. Twenty ml. of water was added and the mixture heated in a water-bath at 85° for two hours. The oily layer solidified, was filtered and dried. The product was recrystallized from methanol yielding 5.0 g. (67%) of white crystals melting at 163–164°. The literature value for N,N'-diphenylpiperazine is 164°.[4]

Acknowledgment.—We wish to thank Dr. Nelson R. Trenner of the Merck Laboratories, Rahway, N. J., for the infrared analysis.

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(1) S. Gabriel, *Ber.*, **21**, 1049 (1888); S. Gabriel and R. Stelzner, *ibid.*, **28**, 2929 (1895).

(2) W. J. Pearlman, THIS JOURNAL, **70**, 871 (1948).

(3) Analyses performed by Clark Microanalytical Laboratory, Urbana, Ill.

(4) D. S. Pratt and C. O. Young, THIS JOURNAL, **40**, 1428 (1918).

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Cyclic Vinyl Ethers as Reagents for the Introduction of Isoprene Units into Organic Compounds

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An extension of the previously described olefin synthesis[2,3] to 3-methyl-2,3-dihydrofuran (V) should offer a convenient method for the stepwise introduction of isoprene units into organic compounds which form Grignard reagents. Likewise, extension of the reaction to 4-methyl-3,4-dihydro-2H-pyran (I) should result in the formation of compounds structurally related to certain natural products (phytol, etc.). The availability[4] of the cyclic vinyl ethers I and V has permitted evaluation of these methods, and this report describes the synthesis of two new alkenols containing isoprene units.

The reaction of isobutylmagnesium bromide with the crude dichloride obtained from I and chlorine resulted in the formation of 2-isobutyl-3-chloro-4-methyltetrahydropyran (III) (35% yield), boiling at 60–75° (4 mm.). The boiling range and varia-

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(1) From the Ph.D. thesis of Howard Holmquist, University of Minnesota, 1951.

(2) *Cf.* (a) M. Jacobson, THIS JOURNAL, **72**, 1489 (1950); (b) R. Paul and O. Riobe, *Compt. rend.*, **224**, 474 (1947).

(3) (a) R. C. Brandon, J. M. Derfer and C. E. Boord, THIS JOURNAL, **72**, 2120 (1950); (b) L. Crombie and S. H. Harper, *J. Chem. Soc.*, 1707 (1950).

(4) W. E. Parham and H. E. Holmquist, THIS JOURNAL, **73**, 913 (1951).