# 1-PHENYL-5(6)-METHYLDIHYDROURACILS AND THEIR TRANSFORMATIONS

R. S. Baltrushis, Z.-I. G. Beresnevichyus, and I. M. Vizgaitis

UDC 547.853.5'854.1'855

The reaction of aniline with methacrylic and crotonic acids gave N-phenyl-α- or β-methyl-β-alanines, which were converted to the corresponding 1-phenyl-5(6)-methyl- and 1-phenyl-2-thioxo-5(6)-methyldihydrouracils by the action of urea or thiocyanates in an acidic medium. The dihydrouracils were converted to ureido acids by the action of alkalis and to N-phenyl-β-alanine hydrazides by the action of hydrazine. 1-Phenyl-2-thioxo-5-methylhexahydropyrimidine was isolated in the reduction of the thioxodihydrouracil. The dihydro- and thioxodihydrouracils react with phosphorus pentasulfide to give 4-thioxo- and 2,4-dithioxodihydrouracils. 1-Phenyl-5(6)-methyldihydrocytosines were obtained from the 4-thioxodihydrouracils. The thioxodihydrouracils were subjected to bromination; 1-(4-bromophenyl)-5(6)-methyldihydrouracils were obtained from 1-phenyl-5(6)-methyldihydrouracils, and 1-phenyl-2-thioxo-5-bromo-5-methyldihydrouracil, which was converted to a uracil by dehydrobromination, was obtained from 1-phenyl-2-thioxo-5-methyldihydrouracil. 1-Phenyl-2-thioxo-5-methyluracil was also obtained by dehydrogenation of 1-phenyl-2-thioxo-5-methyldihydrouracil with sulfur.

N-Substituted β-amino acids and their derivatives are capable of undergoing conversion to heterocyclic compounds, particularly to 1-substituted pyrimidines [1-3]. For the synthesis of these compounds we used N-phenyl-α-methyl- (Ia) and N-phenyl-β-methyl-β-alanine (Ib), which were obtained by the nucleophilic addition of aniline to methacrylic or crotonic acid in toluene [4], as the starting compounds. β-Alanines were converted to 1-phenyl-5- or 6-methyldihydrouracils II by heating with urea in acetic acid with subsequent cyclization with hydrochloric acid [5], while 1-phenyl-2-thioxo-5- or 6-methyldihydrouracils III were obtained by the action of thiocyanates under the same conditions.

In the PMR spectra the protons of the $CH_2$ group of II and III, as well as the products of their subsequent transformation, couple with the proton of the CH group to form the typical AB part of the ABX system. The proton of the CH group also couples with the proton of the methyl group to form a complex multiplet. The signal of an NH group also appears in the spectra in the form of a broad singlet at 8.92 to 9.16 ppm corresponding to one proton. The chemical shifts and the spin–spin coupling constants (SSCC) are presented in Table 1.

TABLE 1. PMR Spectra

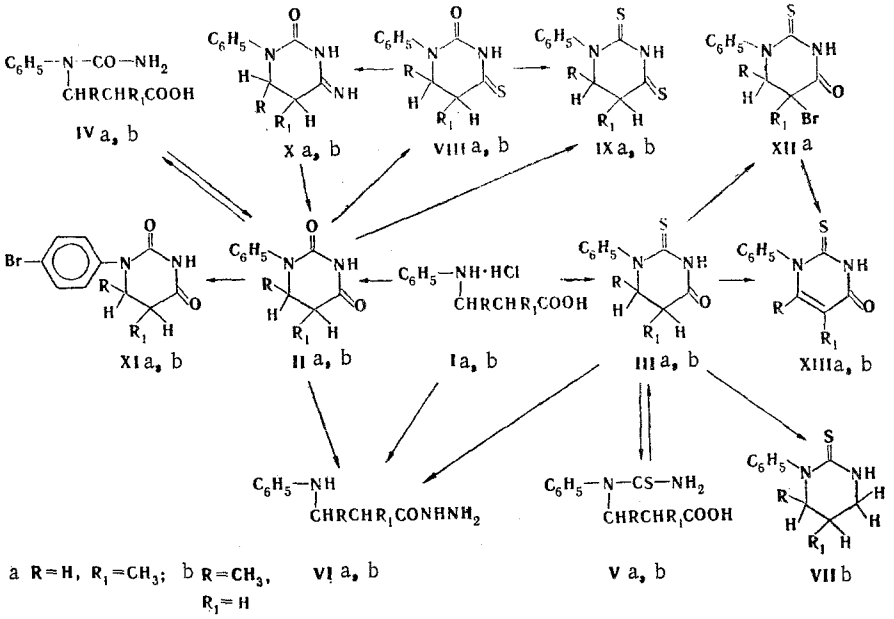
| Compound | δ, ppm | | | |
|---|---|---|---|---|
| | $CH_3$ | $CH_2$ (J, Hz) | CH | aromatic H |
| IIa | 0,91 | 3,26; 3,45 (14, 5,8; 9) | 2,43—2,87 | 6,74—7,11 |
| IIb | 0,86 | 2,35; 2,81 (17,6; 6,4; 5,6) | 3,52—3,91 | 6,72—7,11 |
| IIIa | 0,88 | 3,46; 3,67 (14; 7,4; 10) | 2,54—2,97 | 6,81—7,16 |
| IIIb | 0,92 | 2,46; 2,97 (18; 7,6) | 3,77—4,07 | 6,75—7,07 |
| Xa | 1,23 | 2,67; 3,14 (18, 6,2; 4,8) | 3,65—3,92 | 6,73—7,05 |
| Xb | 0,89 | 2,67 3,14 (18; 6,2; 4,8) | 3,69—3,97 | 6,68—7,07 |
| XIa | 0,91 | 3,24; 3,45 (18,2; 8; 9,8) | 2,43—2,87 | 6,65—7,18 |
| XIb | 0,87 | 2,36; 3,84 (17,6; 6,4; 5,6) | 3,58—3,87 | 6,63—7,24 |
| XIIa | 1,52 | 3,36; 3,79 (15) | — | 6,95 |
| XIIIa | 1,62 | — | — | 7,76—7,17* |
| XIIIb | 1,56 | — | 5,91 | 6,67—7,15 |

*The signals of the protons of the aromatic ring are overlapped by the signals of the proton of the CH group.

A. Snechkus Kaunas Polytechnic Institute, Kaunas 233006. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1097-1101, August, 1981. Original article submitted October 30, 1980.

 0009-3122/81/1708-0816$07.50 

Hexahydropyrimidine compounds II and III undergo decyclization under the influence of nucleophilic reagents: Upon reaction with alkalis they are converted to the corresponding ureido acids IV and V, whereas under the influence of hydrazine they give hydrazides VI, which were also isolated by the action of hydrazine on acids I.




In the case of hydrogenation of thioxodihydrouracils [6] with lithium aluminum hydride in ether or tetrahydrofuran (THF) the keto group in the 4 position is reduced, and 1-phenyl-2-thioxo-6-methylhexahydropyrimidine (VIIb) is obtained from IIIb. A signal of protons of a 4-$CH_2$ group is observed in the PMR spectrum in the form of a multiplet at 3.08-3.31 ppm.

Dihydrouracils II form 4-thioxodihydrouracils VIII when they are heated with $P_2S_5$ in toluene or pyridine [7], while thionation also takes place in the 2 position in the case of more prolonged heating with excess $P_2S_5$ to give 1-phenyl-2,4-dithioxodihydrouracils IX, which were also obtained by thionation of 2-thioxo-III and 4-thioxo derivatives VIII. The IR spectra of IX do not contain an absorption band at 1700 $cm^{-1}$.

1-Aryl-4-thioxodihydrouracils are converted to the corresponding dihydrocytosines in liquid ammonia [8]. In the present research 1-phenyldihydrocytosines X were synthesized by heating 4-thioxodihydrouracils VIII with 25% ammonium hydroxide in an ampul. Depending on the conditions, the dihydrocytosines can exist in the form of imino-amino tautomers with predominance of the imino form. Signals of protons of two unprotonated imino groups at 8.55 and 8.98 ppm are observed in the PMR spectra (in trifluoroacetic acid) of X. Dihydrocytosines X are converted to dihydrouracils II by acid hydrolysis.

It is pointed out in [9, 10] that substitution takes place in the 5 position of the heterocyclic ring when 1-aryldihydrouracils are treated with bromine in acetic acid. We later demonstrated [11, 12] that only the aromatic fragment of the molecule is brominated in the case of bromination of 1-naphthyldihydrouracils under the same conditions. The corresponding 1-(4-bromophenyl)dihydrouracils XI were isolated by bromination of 1-phenyldihydrouracils II. The previously undescribed direct bromination of 2-thioxodihydrouracils was realized, and 1-phenyl-2-thioxo-5-bromo-5-methyldihydrouracil (XIIa), which was dehydrobrominated and converted to 1-phenyl-2-thioxo-5-methyluracil (XIIIa), which was also obtained by dehydrogenation of IIIa with sulfur [13], was isolated.

## EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The PMR spectra of solutions in trifluoroacetic acid were obtained with Hitachi R-22 (90 MHz) and Tesla BS-487C (80 MHz) spectrometers with hexamethyldisiloxane as the internal standard. The individuality of the substances was monitored by means of thin-layer chromatography (TLC) on Silufol UV-254 plates with a loose layer of aluminum oxide and silica gel.

N-Phenyl-α-methyl-β-alanine Hydrochloride (Ia). A mixture of 93 g (1 mole) of aniline, 86 g (1 mole) of methacrylic acid, and 100 ml of dry toluene was heated at 100°C for 24 h, after which it was cooled and made alkaline with 30% NaOH solution. The unchanged aniline was extracted with ether, the alkaline solution was acidified with acetic acid, and the liberated oily mass was separated and dissolved in ether. A stream of dry HCl was passed through the ether solution until it was saturated, after which the mixture was cooled, and the resulting crystals were removed by filtration to give 97 g (46%) of Ia with mp 196-197°C (from ethanol).

N-Phenyl-β-methyl-β-alanine Hydrochloride (Ib). This compound, with mp 176-178°C (from ethanol), was similarly obtained in 48% yield.

1-Phenyl-5-methyldihydrouracil (IIa). A) A mixture of 21.5 g (0.1 mole) of Ia, 12 g (0.2 mole) of urea, and 20 ml of acetic acid was heated at 110°C for 10 h, after which 20 ml of concentrated HCl was added, and heating was continued for another 5 h. Water (30 ml) was then added, and the mixture was allowed to stand at 4°C for 24 h. The precipitated crystals were removed by suction filtration and washed with water and ether to give 14 g of IIa. The characteristics and results of analysis are presented in Tables 1 and 2.

B) A mixture of 2.2 g (0.01 mole) of IVa and 10 ml of concentrated HCl was heated at 100°C for 10 min, after which 20 ml of water was added, and 2 g of IIa was removed by filtration.

C) A mixture of 1 g (5 mmole) of Xa and 5 ml of 18% HCl was heated at 100°C for 20 min, after which it was cooled, and 0.95 g of IIa was removed by filtration.

1-Phenyl-6-methyldihydrouracil (IIb). This compound was obtained from Ib, IVb, and Xb by the methods used to prepare IIa (Table 2).

1-Phenyl-2-thioxo-5-methyldihydrouracil (IIIa). A) A mixture of 21.5 g (0.1 mole) of Ia, 19 g (0.2 mole) of potassium thiocyanate, and 30 ml of acetic acid was heated at 110°C for 8 h, after which 20 ml of concentrated HCl was added, and heating was continued for another 6 h. The mixture was cooled, and the precipitated crystals were removed by filtration and washed with water and ether to give 13.1 g of IIIa (Table 2).

B) A mixture of 1.2 g (5 mmole) of Va and 10 ml of concentrated HCl was heated at 100°C for 10 min, after which 20 ml of water was added, and 1.1 g of IIIa was obtained.

1-Phenyl-2-thioxo-6-methyldihydrouracil (IIIb). This compound was obtained in the same way as IIIa (Table 2).

N-Phenyl-N-carbamido-α-methyl-β-alanine (IVa). A mixture of 2 g (0.01 mole) of IIa and 30 ml of 10% sodium hydroxide was allowed to stand at 20°C for 24 h, after which it was filtered, and the filtrate was acidified to pH 6 with acetic acid. The crystals that were liberated after cooling were removed by filtration and crystallized from ethanol to give 1.6 g of IVa (Table 2).

N-Phenyl-N-carbamido-β-methyl-β-alanine (IVb), N-phenyl-N-thiocarbamido-α-methyl-β-alanine (Va), and N-phenyl-N-thiocarbamido-β-methyl-β-alanine (Vb) were obtained in the same way as IVa (Table 2).

N-Phenyl-α-methyl-β-alanine Hydrazide (IVa). A) A mixture of 2 g (0.01 mole) of IIa, 20 ml of a 25% aqueous solution of hydrazine, and 10 ml of dioxane was heated at 110°C for 10 h, after which 20 ml of water was added, and the mixture was cooled. The mixture was then filtered to give 0.9 g of VIa (Table 2).

B) A mixture of 2.1 g (0.01 mole) of Ia, 1.5 g (0.03 mole) of 99% hydrazine, and 20 ml of dioxane was heated at 100°C for 2 h, after which 30 ml of water was added, and the mixture was allowed to stand at 4°C for a long time to give 1.1 g of VIa.

N-Phenyl-β-methyl-β-alanine Hydrazide (VIb). This compound was obtained in the same way as VIa (Table 2).

1-Phenyl-2-thioxo-6-methylhexahydropyrimidine (VIIb). A 10-g (0.045 mole) sample of IIIb was added in small portions with stirring to a suspension of 2.6 g (0.07 mole) of $LiAlH_4$ in 100 ml of absolute THF, and the mixture was refluxed for 15 h. Ethanol (30 ml) was added, after which the solvents were removed, and the solid mixture was extracted with acetone. A total of 3.1 g of VIIb crystallized out from the extract (Table 2).

TABLE 2. Characteristics of the Synthesized Compounds

| Substance | mp, °C (ethanol) | IR spectrum $\nu$, cm$^{-1}$ | | Found, % | | | Empirical formula | Calc., % | | | Yield, % (method of synthesis) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | NH | C=O | C | H | N | | C | H | N | |
| IIa | 187—189 | 3230 | 1700 | 64,5 | 5,7 | 13,7 | $C_{11}H_{12}N_2O_2$ | 64,7 | 5,9 | 13,7 | 70 (A)<br>100 (B)<br>95 (B) |
| IIb | 167—169 | 3195 | 1725 | 64,5 | 6,0 | 13,8 | $C_{11}H_{12}N_2O_2$ | 64,7 | 5,9 | 13,7 | 65 (A)<br>100 (B)<br>96 (C) |
| IIIa | 184—185 | 3230 | 1700 | 59,8 | 5,6 | 12,7 | $C_{11}H_{12}N_2OS$ | 60,0 | 5,5 | 12,7 | 61 (A)<br>100 (B) |
| IIIb | 196—198 | 3190 | 1715 | 59,7 | 5,4 | 12,6 | $C_{11}H_{12}N_2OS$ | 60,0 | 5,5 | 12,7 | 64 (A)<br>100 (B) |
| IVa | 146—148 | 3455, 3310* | 1725 | 59,2 | 6,5 | 12,7 | $C_{11}H_{14}N_2O_3$ | 59,4 | 6,4 | 12,6 | 72 |
| IVb | 148—151 | 3465, 3325* | 1725 | 59,5 | 6,2 | 12,7 | $C_{11}H_{14}N_2O_3$ | 59,4 | 6,4 | 12,6 | 73 |
| Va | 135—137† | 3440, 3295* | 1710 | 55,6 | 6,1 | 11,9 | $C_{11}H_{14}N_2O_2S$ | 55,4 | 5,9 | 11,8 | 63 |
| Vb | 143—145 | 3430, 3300* | 1720 | 55,6 | 5,8 | 11,8 | $C_{11}H_{14}N_2O_2S$ | 55,4 | 5,9 | 11,8 | 95 |
| VIa | 161—162 | 3305 | 1630 | 62,7 | 8,0 | 21,6 | $C_{10}H_{15}N_3O$ | 62,2 | 7,8 | 21,7 | 63 (A)<br>58 (B) |
| VIb | 119—121 | 3325 | 1635 | 61,9 | 7,9 | 21,6 | $C_{10}H_{15}N_3O$ | 62,2 | 7,8 | 21,7 | 79 (A)<br>46 (B) |
| VIIb | 210—211 | 3205 | | 64,2 | 6,7 | 13,3 | $C_{11}H_{14}N_2$ | 64,0 | 6,8 | 13,6 | 29 |
| VIIIa | 168—170 | 3195 | 1670 | 59,7 | 5,5 | 12,5 | $C_{11}H_{12}N_2O$ | 60,0 | 5,5 | 12,7 | 63 |
| VIIIb | 169—171 | 3200 | 1675 | 59,8 | 5,5 | 12,9 | $C_{11}H_{12}N_2O$ | 60,0 | 5,5 | 12,7 | 72 |
| IXa | 140—142 | 3135 | | 55,9 | 5,2 | 11,7 | $C_{11}H_{12}N_2S_2$ | 55,9 | 5,1 | 11,9 | 68 (A)<br>65 (B),<br>71 (C) |
| IXb | 181—183 | 3120 | | 56,0 | 5,0 | 11,7 | $C_{11}H_{12}N_2S_2$ | 55,9 | 5,1 | 11,9 | 74 (A)<br>62 (B)<br>70 (C) |
| Xa | 221—223‡ | 3325 | 1650 | 65,1 | 6,5 | 21,0 | $C_{11}H_{13}N_3O$ | 65,0 | 6,4 | 20,7 | 74 |
| Xb | 234—236 | 3320 | 1640 | 65,1 | 6,8 | 20,9 | $C_{11}H_{13}N_3O$ | 65,0 | 6,4 | 20,7 | 84 |
| XIa | 186—189 | | | 46,5 | 4,1 | 10,0 | $C_{11}H_{11}BrN_2O_2$ | 46,7 | 3,9 | 9,9 | 80 |
| XIb | 182—185 | | | 46,4 | 3,8 | 9,9 | $C_{11}H_{11}BrN_2O_2$ | 46,7 | 3,9 | 9,9 | 71 |
| XIIa | 168—170 | | | 44,3 | 3,9 | 9,1 | $C_{11}H_{14}BrN_2OS$ | 44,2 | 3,7 | 9,4 | 27 |
| XIIIa | 205—208 | 3170 | 1675 | 60,4 | 4,8 | 13,2 | $C_{11}H_{10}N_2OS$ | 60,5 | 4,6 | 12,8 | 18 (A)<br>98 (B) |
| XIIIb | 233—236 | 3195 | 1700 | 60,4 | 4,4 | 12,4 | $C_{11}H_{10}N_2OS$ | 60,5 | 4,6 | 12,8 | 13 |

*Absorption of the NH and OH groups. †Chloroform.
‡Dioxane. **Dimethyl sulfoxide (DMSO).

1-Phenyl-4-thioxo-5-methyldihydrouracil (VIIIa). A mixture of 2 g (0.01 mole) of IIa, 1.65 g (0.075 mole) of $P_2S_5$, and 10 ml of dry pyridine was heated at 115°C for 5 h, after which 10 ml of water was added, and the mixture was allowed to stand at 20°C for 18 h. The resulting yellow precipitate was removed by filtration and crystallized from ethanol to give 1.4 g of VIIIa (Table 2).

1-Phenyl-4-thioxo-6-methyldihydrouracil (VIIIb). This compound was similarly obtained (Table 2).

1-Phenyl-2,4-dithioxo-5-methyldihydrouracil (IXa). A) A mixture of 2.2 g (0.01 mole) of IIIa, 2.2 g (0.01 mole) of $P_2S_5$, and 15 ml of dry pyridine was heated at 115°C for 10 h, after which 10 ml of water was added, and 1.5 g of IXa was isolated (Table 2) .

B) A total of 1.5 g of IXa was isolated from the reaction of 2 g (0.01 mole) of IIa and 3.3 g (0.015 mole) of $P_2S_5$ by heating for 12 h as in method A.

C) Compound IXa was obtained as in method A from 2.2 g (0.01 mole) of VIIIa and 2.2 g (0.01 mole) of $P_2S_5$.

1-Phenyl-2,4-dithioxo-6-methyldihydrouracil (IXb). This compound was obtained by the method used to prepare IXa.

1-Phenyl-5-methyldihydrocytosine (Xa). A mixture of 2.2 g (0.01 mole) of VIIIa and 30 ml of 25% ammonium hydroxide was heated in a sealed ampul at 60°C for 4 h, after which it was cooled, and 1.5 g of Xa was removed by filtration (Table 2).

1-Phenyl-6-methyldihydrocytosine (Xb). This compound was obtained by the method used to prepare Xa (Table 2).

1-(4-Bromophenyl)-5-methyldihydrouracil (XIa). A solution of 4.8 g (0.03 mole) of bromine in 10 ml of acetic acid was added dropwise with stirring at 100°C to a solution of

4 g (0.02 mole) of IIa and 1.6 g of sodium acetate in 30 ml of acetic acid, after which the mixture was allowed to stand for 18 h. It was then diluted with water (1:1), and the precipitated crystals were removed by filtration and crystallized from ethanol to give 4.5 g of XIa (Table 2).

1-(4-Bromophenyl)-6-methyldihydrouracil (XIb). This compound was obtained by the method used to prepare XIa (Table 2).

1-Phenyl-2-thioxo-5-bromo-5-methyldihydrouracil (XIIa). A 4.4-g (0.02 mole) sample of IIIa was dissolved at 100°C in 30 ml of acetic acid, a solution of 6.3 g (0.04 mole) of bromine in 10 ml of acetic acid was added dropwise with stirring, and the mixture was stirred for 5 h. Water (50 ml) was added, the mixture was cooled, and the resulting precipitate was removed by filtration and crystallized from ethanol to give 0.8 g of XIIa (Table 2).

1-Phenyl-2-thioxo-5-methyluracil (XIIIa). A) A mixture of 2.2 g (0.01 mole) of IIIa and 5 g of sulfur was heated at 220°C for 3 h, after which it was cooled, pulverized, and extracted with 10% sodium hydroxide solution. The extract was filtered and acidified to pH 5 with dilute (1:3) HCl. The resulting yellow substance was removed by filtration and crystallized from ethanol to give 0.3 g of XIIIa (Table 2).

B) A mixture of 0.15 g (5 mmole) of XIIa, 0.1 g of lithium chloride, and 3 ml of dimethylformamide was heated at 120°C for 4 h, after which 2 ml of water was added, and the resulting precipitate was removed by filtration and washed with water to give 0.1 g of XIIIa (Table 2).

## LITERATURE CITED


1. R. S. Baltrushis, A. N. Machyulis, Z.-I. G. Beresnevichyus, and M. I. Pugina, USSR Inventor's Certificate No. 173922; Byull. Izobret., No. 16, 79 (1965).
2. B. M. Kovarskaya, V. V. Gur'yanova, R. S. Baltrushis, and Z.-I. G. Beresnevichyus, USSR Inventor's Certificate No. 332114; Byull. Izobret., No. 10, 97 (1972).
3. M. F. Mechinskas, Z.-I. G. Beresnevichyus, and R. S. Baltrushis, USSR Inventor's Certificate No. 421709; Byull. Izobret., No. 12, 81 (1974).
4. U.S. Patent No. 6515519; Chem. Abstr., 68, 2738 (1968).
5. R. S. Baltrushis and I. I. Marioshyus, USSR Inventor's Certificate No. 197595; Byull. Izobret., No. 13, 33 (1967).
6. R. S. Baltrushis, I. I. Marioshyus, and Z.-I. G. Beresnevichyus, USSR Inventor's Certificate No. 232269; Byull. Izobret., No. 1, 28 (1969).
7. V. Škaric, B. Gaspert, I. Jerkunica, and D. Škaric, Croat. Chem. Acta, 37, 199 (1965).
8. D. M. Brown and M. J. E. Hewlins, J. Chem. Soc., C, No. 16, 2050 (1968).
9. N. W. Gabel and S. B. Binkley, J. Org. Chem., 23, 643 (1958).
10. R. S. Baltrushis and I. I. Marioshyus, Khim. Geterotsikl. Soedin., No. 1, 120 (1969).
11. R. S. Baltrushis and Z.-I. G. Beresnevichyus, Khim. Geterotsikl. Soedin., No. 12, 1695 (1971).
12. R. S. Baltrushis, Z.-I. G. Beresnevichyus, and A. I. Zubene, Khim. Geterotsikl. Soedin., No. 4, 524 (1971).
13. B. R. Baker and J. L. Kelley, J. Med. Chem. Soc., 11, 682 (1968).