ISSN 1070-4280, Russian Journal of Organic Chemistry, 2008, Vol. 44, No. 12, pp. 1760–1764. © Pleiades Publishing, Ltd., 2008.
Original Russian Text © K.M. Bormasheva, O.N. Nechaeva, I.K. Moiseev, 2008, published in Zhurnal Organicheskoi Khimii, 2008, Vol. 44, No. 12, pp. 1786–1790.

Reactions of Adamantyl-Substituted Keto Esters with Hydrazine and Phenylhydrazine

K. M. Bormasheva[a], O. N. Nechaeva[b], and I. K. Moiseev[a]

[a] *Samara State Technical University, ul. Molodogvardeiskaya 244, Samara, 443100 Russia*
e-mail: ikmoiseev@mail.ru

[b] *Samara State University, Samara, Russia*

Received June 5, 2007

Abstract—Reactions of adamantyl-substituted keto and diketo carboxylic acid esters with hydrazine and phenylhydrazine were studied. Ethyl 3-(1-adamantyl)-2-(1-adamantylcarbonyl)-3-oxopropanoate reacted with hydrazine to give ethyl 3,5-di(1-adamantyl)-1*H*-pyrazole-4-carboxylate. Reactions of ethyl 2-(1-adamantylcarbonyl)-3-oxobutanoate and ethyl 4-(1-adamantyl)-3-oxo-2-(1-oxoethyl)butanoate with hydrazine and phenylhydrazine followed a complicated pattern and led to the formation of mixtures of the corresponding hydrazides and pyrazolones.

DOI: 10.1134/S1070428008120063

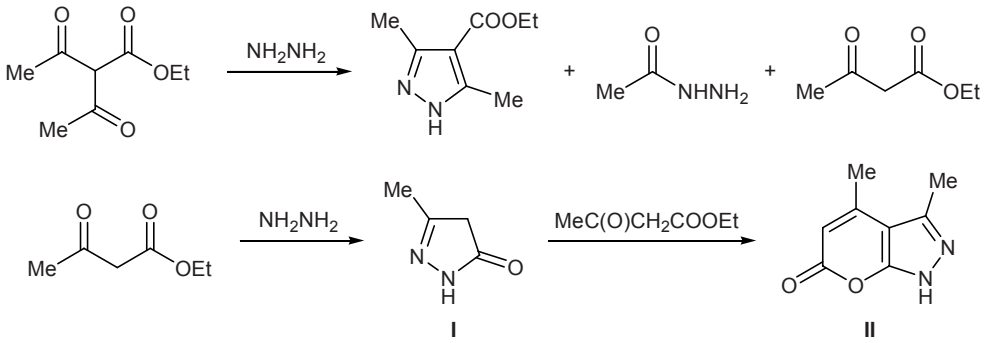
Among numerous reactions of keto carboxylic acid esters, reactions with hydrazine and its derivatives were studied in most detail. The reaction of ethyl 3-oxo-2-(1-oxoethyl)butanoate with hydrazine gives a mixture of ethyl 3,5-dimethyl-1*H*-pyrazole-4-carboxylate, 3-methyl-1*H*-pyrazol-5-one (**I**), and 3,4-dimethylpyrano[2,3-*c*]pyrazol-6(1*H*)-one (**II**) [1–3] (Scheme 1). Adamantyl-substituted keto esters **IIIa** and **IIIb** were converted into *N*-phenylpyrazolones **IVa** and **IVb** by treatment with phenylhydrazine [4, 5] (Scheme 2).

The goal of the present work was to examine the behavior of previously synthesized adamantyl-substituted keto and diketo carboxylic acid esters [6] in reactions with hydrazine and phenylhydrazine. Esters **IIIa** and **IIIb** reacted with hydrazine hydrate according to Scheme 2, and the products were adamantyl-substituted pyrazolones **Va** and **Vb** whose structure was confirmed by spectral data.

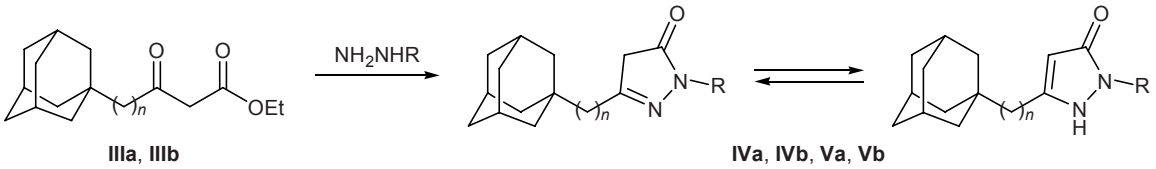
In the reaction of ethyl 3-(1-adamantyl)-2-(1-adamantylcarbonyl)-3-oxopropanoate (**VI**) with hydrazine hydrate, the cyclization involved both carbonyl groups, and the only product was ethyl 3,5-di(1-adamantyl)-1*H*-pyrazole-4-carboxylate (**VII**) (Scheme 3); the structure of ester **VII** was consistent with its spectral parameters.

Unsymmetrical diketo esters, ethyl 2-(1-adamantylcarbonyl)-3-oxobutanoate (**VIIIa**) and ethyl 4-(1-adamantyl)-3-oxo-2-(1-oxoethyl)butanoate (**VIIIb**) reacted with hydrazine and phenylhydrazine in a complicated fashion, and these reactions gave mixtures of products. In the reaction of compound **VIIIa** with

Scheme 1.

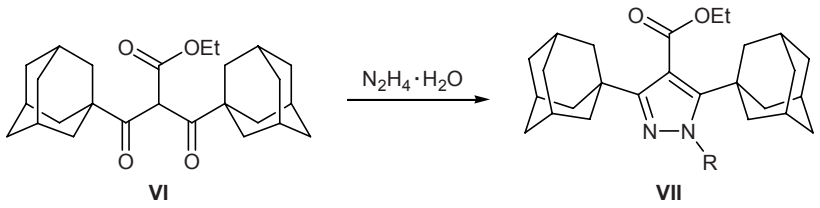


Scheme 2.



n = 0 (**a**), 1 (**b**); **IV**, R = Ph; **V**, R = H.

Scheme 3.

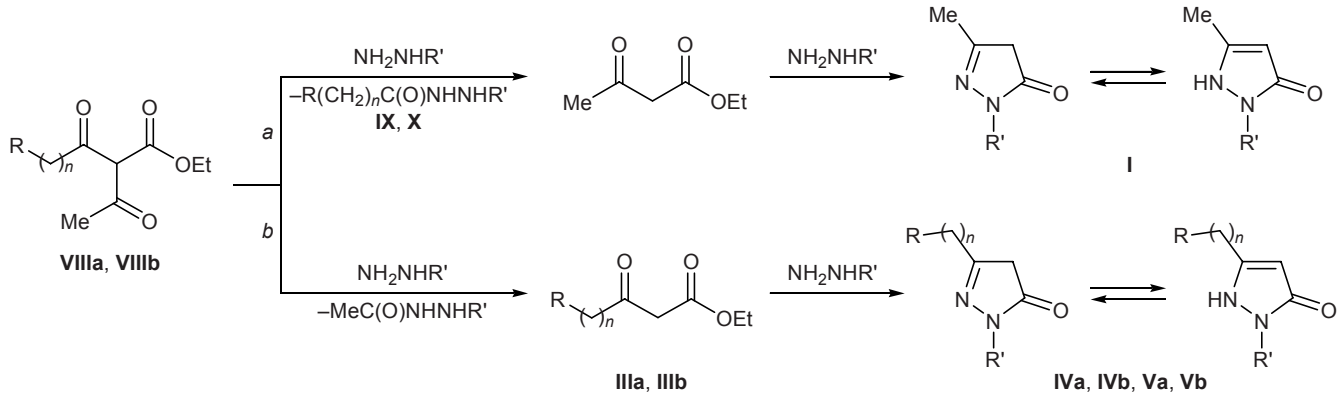


hydrazine at ratios of 1:1.5, 1:6, and 1:9, the products were 3-methyl-1*H*-pyrazol-5-one (**I**), 3-(1-adamantyl)-1*H*-pyrazol-5-one (**Va**), and adamantane-1-carbohydrazide (**IX**). The reaction of **VIIIa** with phenylhydrazine gave *N*′-phenyladamantane-1-carbohydrazide (**X**) as the major product and a small amount of ethyl 3-(1-adamantyl)-5-methyl-1-phenyl-1*H*-pyrazole-4-carboxylate. Ester **VIIIb** reacted with hydrazine and phenylhydrazine to give, respectively, 3-(1-adamantylmethyl)-1*H*-pyrazol-5-one (**Vb**) and 3-(1-adamantylmethyl)-1-phenyl-1*H*-pyrazol-5-one (**IVb**) together with acetohydrazide. Taking into account published data [7], the formation of the above products in the reactions of esters **VIIIa** and **VIIIb** with hydrazine and phenylhydrazine may be illustrated by Scheme 4.

Paths *a* and *b* are equally probable for compound **VIIIa**, whereas path *b* predominates in the reaction with **VIIIb**. This is consistent with the results of quantum-chemical calculations of charges on the carbonyl carbon atoms in molecules **VIIIa** and **VIIIb**. The charges on the carbonyl carbon atoms in **VIIIa** are similar (0.26); therefore, the probability for attack by hydrazine molecule on the acetyl carbonyl group (path *b*) is the same as that for attack at the adamantylcarbonyl fragment (path *a*). In contrast, the positive charge on the acetyl carbonyl carbon atom in molecule **VIIIb** (0.27) is larger than that on the carbonyl carbon atom neighboring to the adamantyl fragment (0.22), so that attack by hydrazine molecule on the former seems to be more probable, and the products are acetohydrazide and ethyl 4-(1-adamantyl)-3-oxobutanoate (**IIIb**).

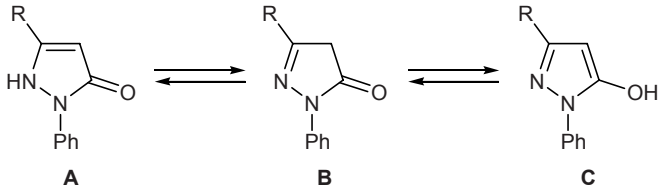
It is known that 3-substituted pyrazolone derivatives can exist as three tautomers **A**–**C** (Scheme 5); however, tautomer **A** is commonly preferred [8]. The ^{1}H NMR spectra of compounds **IVa**, **IVb**, **Va**, and **Vb** (DMSO-d_6) contained a one-proton singlet in the region δ 5.15–5.34 ppm, which was assigned to 4-H, and a broadened singlet in the region δ 10.2–11.48 ppm

Scheme 4.



n = 0 (**a**), 1 (**b**); **IV**, **X**, R = 1-adamantyl, R′ = Ph; **V**, **IX**, R = 1-adamantyl, R′ = H.

Scheme 5.



(1H, NH in **IVa** and **IVb**; 2H, NH in **Va** and **Vb**). In the spectra of **IVa** and **IVb**, recorded from solutions in $CDCl_3$, we observed a two-proton singlet at δ 3.35–3.40 ppm due to protons in position *4* of the pyrazole ring, while no signal was present in the region δ 10.00–11.50 ppm. We failed to obtain ^{1}H NMR spectra of compounds **Va** and **Vb** in $CDCl_3$ because of their poor solubility in that solvent. These findings suggest that compounds **IVa**, **IVb**, **Va**, and **Vb** in the crystalline state and in polar solvents have structure **A** and that tautomer **B** prevails in nonpolar solvents.

EXPERIMENTAL

The IR spectra were recorded from samples prepared as KBr pellets on a Shimadzu FTIR-8400S instrument. The ^{1}H NMR spectra were measured on a Bruker AM-300 instrument at 300 MHz using tetramethylsilane as internal reference. The mass spectra were obtained on a Finnigan Trance DCQ GC–MS system (USA). The elemental compositions were determined on a TermoFinnigan Flash 1112 NCH analyzer. Column chromatography was performed using Silicagel 60 (0.063–0.200 mm). The purity of the products was checked by TLC on Armsorb KSKG and Silufol UV 254 plates; spots were visualized by treatment with iodine vapor.

Quantum-chemical calculations were performed using HyperChem 5 software. Geometric parameters were optimized by semiempirical methods (AM1 parameterization); analogous results were obtained in terms of MNDO and PM3 approximations.*

Initial esters **IIIa** and **IIIb** were synthesized according to [4, 5], and diketo esters **VIIIa** and **VIIIb** were prepared as reported in [6].

Reactions of keto esters IIIa and IIIb with hydrazine hydrate. A solution of 4 mmol of ester **IIIa** or **IIIb** in 2 ml of ethanol was added dropwise on cooling to a solution of 0.8 g (16 mmol) of hydrazine hydrate in 2 ml of ethanol. The mixture was stirred and left to stand overnight. The precipitate was filtered off, washed with 2 ml of ethanol, and recrystallized from ethanol.

3-(1-Adamantyl)-1*H*-pyrazol-5-one (Va). Yield 0.54 g (63%), colorless crystals, mp 292.5–295.5°C, R_f 0.18 (Armsorb, $CHCl_3$–MeOH, 10:1 by volume). IR spectrum, ν, cm^{-1}: 1600 (C=O); 2850, 2904 (C–H_{Ad}); 3444 (N–H). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.42 m (6H, Ad), 1.75 s (6H, Ad), 1.92 s (3H, Ad), 5.15 s (1H, CH), 10.20 br.s (2H, NH). Found, %: C 71.49; H 8.19; N 12.90. $C_{13}H_{18}N_2O$. Calculated, %: C 71.56; H 8.26; N 12.84.

3-(1-Adamantylmethyl)-1*H*-pyrazol-5-one (Vb). Yield 0.44 g (47%), colorless plates, mp 306–308°C, R_f 0.46 (Armsorb, $CHCl_3$–MeOH, 5:1 by volume). IR spectrum, ν, cm^{-1}: 1604 (C=O); 2846, 2902 (C–H_{Ad}); 3421 (NH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.44 s (6H, Ad), 1.60 m (6H, Ad), 1.91 s (3H, Ad), 2.19 s (2H, Ad**CH**$_2$), 5.15 s (1H, CH), 10.20 br.s (2H, NH). Found, %: C 72.21; H 8.77; N 11.94. $C_{14}H_{20}N_2O$. Calculated, %: C 72.38; N 8.68; N 12.06.

3-(1-Adamantyl)-1-phenyl-1*H*-pyrazol-5-one (IVa) was synthesized according to the procedure described in [4]. Yellow crystals, mp 140–141.5°C; published data [4]: mp 138–139°C; R_f 0.39 (Silufol, CCl_4–Me_2CO, 10:1 by volume). IR spectrum, ν, cm^{-1}: 1593 (C=C_{arom}); 1716 (C=O); 2850, 2908 (C–H_{Ad}); 3448 (NH). ^{1}H NMR spectrum, δ, ppm: in DMSO-d_6: 1.66 s (6H, Ad), 1.82 m (6H, Ad), 1.95 s (3H, Ad), 5.34 s (1H, 4-H), 7.10 t (1H, H_{arom}, J = 6.90 Hz), 7.30 t (2H, H_{arom}, J = 7.20 Hz), 7.60 d (2H, H_{arom}, J = 7.50 Hz), 11.48 br.s (1H, NH); in $CDCl_3$: 1.70 q (6H, Ad), 1.81 s (6H, Ad), 2.02 s (3H, Ad), 3.35 s (2H, 4-H), 7.09 t (1H, H_{arom}, J = 7.85 Hz), 7.32 t (2H, H_{arom}, J = 7.80 Hz), 7.83 d (2H, H_{arom}, J = 8.10 Hz). Found, %: C 77.55; H 7.49; N 9.50. $C_{19}H_{22}N_2O$. Calculated, %: C 77.52; H 7.53; N 9.52.

3-(1-Adamantylmethyl)-1-phenyl-1*H*-pyrazol-5-one (IVb) was synthesized according to the procedure described in [5]. Yellow crystals, mp 196–197°C; published data [5]: mp 192–193°C; R_f 0.53 (Silufol;

* The calculations were performed by E.A. Bakhmatova (Zelinskii Institute of Organic Chemistry, Russian Academy of Sciences, Moscow, Russia).

CCl_4–Me_2CO, 4:1 by volume). IR spectrum, ν, cm^{-1}: 1593 (C=C_{arom}); 1689 (C=O); 2846, 2900 (C–H_{Ad}); 3440 (NH). ^1H NMR spectrum, δ, ppm: in DMSO-d_6: 1.53 m (12H, Ad), 1.86 s (3H, Ad), 2.15 s (2H, AdC**H_2**), 5.25 s (1H, 4-H), 7.15 t (1H, H_{arom}, J = 7.65 Hz), 7.36 t (2H, H_{arom}, J = 7.65 Hz), 7.75 d (2H, H_{arom}, J = 8.10 Hz), 11.38 br.s (1H, NH); in $CDCl_3$: 1.67 m (9H, Ad), 2.00 s (6H, Ad), 2.25 s (2H, AdC**H_2**), 3.40 s (2H, 4-H), 7.20 m (1H, H_{arom}), 7.40 m (2H, H_{arom}), 7.80 m (2H, H_{arom}). Found, %: C 76.47; H 8.82; N 6.86. $C_{20}H_{24}N_2O$. Calculated, %: C 76.41; H 8.83; N 6.80.

Ethyl 3-(1-adamantyl)-2-(1-adamantylcarbonyl)-3-oxopropanoate (VI). Finely cut metallic sodium, 0.70 g (30 mmol), was added under stirring to a mixture of 7.56 g (30 mmol) of ethyl 3-(1-adamantyl)-3-oxopropanoate (**IIIa**) and 60 ml of anhydrous diethyl ether, and the mixture was left to stand for 24 h. It was then cooled in an ice bath, a solution of 6.00 g (30 mmol) of adamantane-1-carbonyl chloride in 24 ml of anhydrous diethyl ether was added dropwise, and the mixture was stirred and left overnight. The mixture was acidified with a small amount of 5% sulfuric acid, ~50 ml of water was added, the mixture was stirred, and the ether layer was separated, washed with a 5% solution of sodium hydrogen carbonate and water, and dried over sodium sulfate. The solvent was distilled off, and the residue was recrystallized from hexane. Yield 4.64 g (37%), colorless crystals, mp 115–118°C, R_f 0.76 (Armsorb, $CHCl_3$–MeOH, 15:1 by volume). IR spectrum, ν, cm^{-1}: 1691, 1706 (C=O, ketone); 1730 (C=O, ester); 2905, 2850 (C–H_{Ad}). ^1H NMR spectrum, δ, ppm: 1.17 t (3H, CH_3, J = 5.35 Hz), 1.68 s (12H, Ad), 1.75 s (12H, Ad), 2.00 s (6H, Ad), 4.15 q (2H, OCH_2, J = 5.39 Hz), 5.75 s (1H, CH). Found, %: C 75.64; H 8.66. $C_{26}H_{36}O_4$. Calculated, %: C 75.73; H 8.74.

Reaction of diketo ester VI with hydrazine hydrate. A solution of 0.15 g (3 mmol) of hydrazine hydrate in 2 ml of ethanol was mixed on cooling with 0.80 g (2 mmol) of ester **VI** in 5 ml of ethanol. The mixture was stirred and left overnight, additional 5 ml of ethanol and 0.15 g (3 mmol) of hydrazine hydrate were added, and the mixture was again stirred and left overnight. The solvent was distilled off, the residue was treated with a small amount of water, and the precipitate was filtered off and recrystallized from ethanol. Yield of ethyl 3,5-di(1-adamantyl)-1*H*-pyrazole-4-carboxylate (**VII**) 0.68 g (86%), colorless crystals, mp 270–273°C, R_f 0.23 (Armsorb, $CHCl_3$–MeOH, 15:1, by volume). IR spectrum, ν, cm^{-1}: 1712 (C=O); 2850, 2904 (C–H_{Ad}); 3259, 3417 (NH). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.24 t (3H, CH_3, J = 6.75 Hz), 1.62 t (12H, Ad, J = 13.05 Hz), 1.88 d (18H, Ad, J = 16.05 Hz), 4.16 q (2H, OCH_2, J = 7.00 Hz), 12.12 br.s (1H, NH). Found, %: C 76.47; H 8.82; N 6.86. $C_{26}H_{36}N_2O_2$. Calculated, %: C 76.41; H 8.83; N 6.80.

Reaction of diketo ester VIIIa with hydrazine hydrate. A solution of 0.38 g (7.5 mmol) of hydrazine hydrate in 2 ml of ethanol was mixed on cooling with 1.46 g (5 mmol) of ester **VIIIa** in 2 ml of ethanol, and the mixture was stirred and left overnight. The solvent was distilled off, and the residue was separated by column chromatography using chloroform–methanol (15:1 by volume) as eluent to isolate 0.16 g (11%) of pyrazolone **I**, (colorless crystals, mp 220–224°C; published data [7]: mp 223–224°C), 0.37 g (25%) of 3-(1-adamantyl)-1*H*-pyrazol-5-one (**Va**) (colorless crystals, mp 289–291°C) and 0.35 g (24%) of adamantane-1-carbohydrazide (**IX**) (colorless crystals, mp 154–157°C; published data [9]: mp 156–157°C).

Following an analogous procedure, reactions of **VIIIa** with 1.50 g (30 mmol) and 2.25 g (45 mmol) of hydrazine hydrate were performed.

Reaction of diketo ester VIIIb with hydrazine hydrate. Hydrazine hydrate, 1.50 g (30 mmol), was added to a solution of 1.53 g (5 mmol) of ester **VIIIb** in 15 ml of ethanol, and the mixture was heated for 4 h under reflux. The solvent was distilled off under reduced pressure (water-jet pump), and the residue was recrystallized from ethanol. Yield of **Vb** 0.45 g (39%), colorless plates, mp 306–308°C.

Reactions of diketo esters VIIIa and VIIIb with phenylhydrazine. A mixture of 5 mmol of ester **VIIIa** or **VIIIb** and 0.65 g (6 mmol) of phenylhydrazine was heated for 2 h at 70°C on a water bath, 2 ml of ethanol was added to the hot mixture, and the mixture was left overnight. The precipitate was filtered off and washed with 3 ml of ethanol.

In the reaction with ester **VIIIa**, the product was *N*-phenyladamantane-1-carbohydrazide (**X**). Yield 1 g (74%), colorless crystals, mp 226–228°C, R_f 0.29 (Silufol, CCl_4–Me_2CO, 10:1 by volume). IR spectrum, ν, cm^{-1}: 1600 (C=C_{arom}); 1641 (C=O); 2850, 2900 (C–H_{Ad}); 3298, 3344 (NH). ^1H NMR spectrum, δ, ppm: 1.70 s (6H, Ad), 1.88 m (6H, Ad), 2.00 s (3H, Ad), 6.70 d (3H, H_{arom}, J = 6.00 Hz), 7.10 t (2H, H_{arom}, J = 6.30 Hz), 7.45 br.s (1H, NH), 9.35 s (1H, NH). Found, %: C 71.05; H 8.09; N 10.45. $C_{17}H_{22}N_2O$. Calculated, %: C 71.11; H 8.15; N 10.37.

The residue obtained after evaporation of the filtrate was (according to the GC–MS data) a mixture of 86% of ethyl 3-(1-adamantyl)-5-methyl-1-phenyl-1*H*-pyrazole-4-carboxylate and 14% of unidentified substances.

In the reaction with ester **VIIIb** we isolated 0.42 g (27%) of compound **IVb** as yellow crystals with mp 196–197°C; published data [5]: mp 192–193°C.

REFERENCES

1. Rosengarten, G.D., *Justus Liebigs Ann. Chem*., 1894, vol. 279, p. 237.
2. Seidel, F., *Chem. Ber*., 1932, vol. 65, p. 1205.
3. Seidel, F., *Chem. Ber*., 1935, vol. 68, p. 1913.
4. Stetter, H. and Rauscher, E., *Chem. Ber*., 1960, vol. 93, p. 2054.
5. Stepanov, F.N., Sidorova, L.I., and Dovgan', N.A., *Zh. Org. Khim*., 1972, vol. 8, p. 1834.
6. Bormasheva, K.M., Nechaeva, O.N., Lyzhov, V.V., Pozdnyakov, V.V., and Moiseev, I.K., *Izv. Vyssh. Uchebn. Zaved., Ser. Khim. Khim. Tekhnol*., 2005, vol. 48, no. 10, p. 47.
7. Jae-Chul Jung, Watkins, B.E., and Avery, M.A., *Tetrahedron*, 2002, vol. 58, p. 3639.
8. Joule, J.A. and Mills, K., *Heterocyclic Chemistry*, Malden, MA: Blackwell Science, 2000, 4th ed.
9. Stetter, H. and Rauscher, E., *Chem. Ber*., 1960, vol. 93, p. 1161.