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Studies on the Reaction between Polynitrobenzene Compounds and Active Methylene Groups. IX.[1] On the Janovsky Complexes derived from Some 1-Substituted 2,4,6-Trinitrobenzene Derivatives[2]

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Janovsky reaction of picrylchloride (PC) performed in the acetone solution containing sodium methoxide gave the Janovsky complex (Ic) and no evidence of the formation of an alternative one (IIc) was obtainable. 2,4,6-Trinitroanisole (TNA) also gave the analogus result. In the case of sodium 2,4,6-trinitrobenzene-1-sulfonate, Id was the major complex and the other one (IId) was also formed. The stability of the Janovsky complexes of 1,3,5-trinitrobenzene (TNB), PC and TNA were studied and their large stability constants were noticed. The ratios of the formation constants, K_{TNB}/K_{TNA}, K_{TNB}/K_{PC} and K_{PC}/K_{TNA}, were determined as 3.3, 1.6 and 2.1, respectively.

In the preceeding paper[1] it was discussed with respect to the chemical structure of the Janovsky complex derived from 2,4,6-trinitroanisole (TNA) and acetone, that Ib was more reasonable than IIb. It may be considered from the point of view of the sterical requirement that Ib must be less stable than IIb. Nevertheless Ib was isolated from the reaction mixture and IIb could not be detected. The present paper deals with the structural elucidation of the Janovsky complexes of 1,3,5-trinitrobenzene (TNB) derivatives having the effective leaving groups, such as picrylchloride (PC) and sodium 2,4,6-trinitrobenzene-1-sulfonate (Na-TNB-S). The stabilities of the Janovsky complexes of TNB, PC and TNA are also discussed.

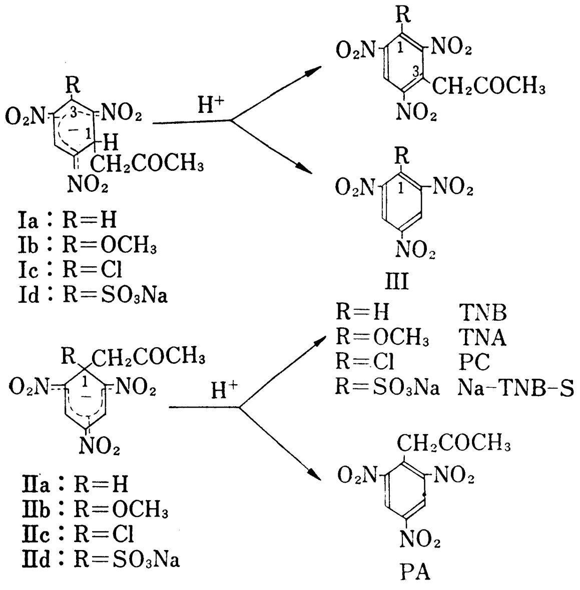

Chart 1

Formerly, one of the authors isolated 3-acetonyl-PC from the solution of Janovsky reaction of PC in acetone.[4] He also detected the spot on paper partition chromatogram having the same developed color and *Rf* value as those due to picrylacetone (PA). From these results it was considered that PC might form Janovsky complex mainly at C-3 position giving

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[1] Part VIII: M. Kimura, N. Obi and M. Kawazoi, *Chem. Pharm. Bull.* (Tokyo), **17**, 531 (1969).

[2] A part of this paper concerning the structure of the Janovsky complexes, was presented at the Meeting of the Hokkaido Branch of the Japan Society for Analytical Chemistry, Feb. 1968 and the other part at the 42nd Meeting of the Hokkaido Branch of the Pharmaceutical Society of Japan, Nov. 1969.

[3] Location: *Nishi-6-chome, Kita-12-jo, Sapporo.*

[4] M. Kimura, *Pharm. Bull.* (Tokyo), 3, 75 (1955).

Table I. Relative Retention Time of TNB Derivatives$^{a)}$

Compound	Relative retention time	
	1.5% SE-30	3% OV-17
TNB	0.78	0.76
PC	1.00 (3.0 min)	1.00 (3.9 min)
TNA	1.12	1.00
PA	3.01	2.42
3-Acetonyl-PC	3.35	2.83
3-Acetonyl-TNA	3.52	3.05

a) Analytical condition is given in experimental part.

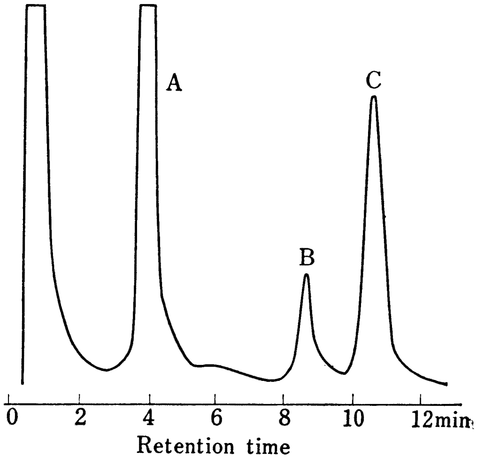

Fig. 1. Gas Liquid Chromatography of Products from the Acidified Janovsky Complex of PC

A: PC, B: 3-acetonyl-4,6-dinitro-chlorobenzene, C: 3-acetonyl-PC

Ic and partly at C-1 giving IIc. Recently Foster, *et al.* reported5) that the nuclear magnetic resonance(NMR) spectrum of the Janovsky reaction mixture of PC, acetone and triethylamine was consistent with Ic and was in conflict with IIc. Thus the isolation of the Janovsky complex of PC was undertaken by the method1) formerly established. NMR spectrum of this complex agreed with the Foster's observation. Thin-layer(TL) chromatogram of the acidified reaction mixture, however, gave a spot very similar to that of PA, in addition to that due to 3-acetonyl-PC. This showed the possibility of the existence of IIc in addition to that of Ic and further investigation was carried out by using gas liquid chromatography(GLC). TNB derivatives are explosive in general. Nevertheless there was no trouble by the use of 3% OV-17 or 1.5% SE-30 column. Table I shows relative retention times of TNB derivatives to PC under the established condition given in the experimental section. The result of OV-17 GLC of the products obtained from the acidified Janovsky complex of PC is shown in Fig. 1. No peak corresponding to PA was detectable. In order to separate the compound corresponding to peak B, Janovsky complex prepared from 10 g of PC was treated with hydrochloric acid and the products were chromatographed on silica gel and then on polyamide. Despite of the careful treatment no PA was obtained but 0.14 g of colorless needles, mp 98°, having the same *Rf* value and color on TL chromatogram as those due to PA, was isolated. It was identified with 3-acetonyl-4,6-dinitrochlorobenzene6) on the basis of the elemental analysis, NMR spectroscopy and melting point.7) Therefore, it may be concluded that the Janovsky complex derived from PC is Ic and the formation of IIc is highly questionable.

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5) R. Foster, C.A. Fyfe and (in part) P.H. Emslie and M.I. Foreman, *Tetrahedron*, **23**, 227 (1967).

6) The mechanism of the formation of this compound may be as follows:

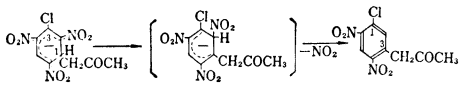


Chart 2

In this mechanism the departure and the attack of hydride ion may occur in solvent cage and hydride ion may attack C-2 for the release of sterical hindrance. This may be coincident with the fact that 3-acetonyl-2,6-dinitrochlorobenzene was unable to detect in this experiment.

7) W. Borsche and H. Bahr, *Ann.*, **402**, 81 (1914).

In general, Meisenheimer type compounds are stable in dipolar aprotic solvent and less stable in prortic one. Janovsky reaction of PC was carried out in acetone-methanol mixture in the range of 10—90% methanol content, with the subsequent treatment in the same way as mentioned above. In all cases 3-acetonyl-PC was detected besiders PC and TNA which was formed from PC by the attack of methoxide ion. No evidence was obtained for the presence of PA also in these cases. GLC of the products[8] from the Janovsky reaction of TNA showed similar results, namely PA could not but 3-acetonyl-TNA be detected. This seems to indicate that the Janovsky complex of TNA is Ib and supports the results in the preceeding report.[1]

As the Janovsky reaction of Na-TNB-S gave very unstable color, the complex was hardly to be obtainable. After acid treatment of the reaction mixture, however, PA was detected by TL chromatography (TLC) and GLC. By column chromatography on polyamide, 5 mg of PA and 45 mg of colorless needles having *Rf* 0.5 on TLC[9] were obtained from 176 mg of Na-TNB-S$\cdot$2H$_2$O. The new compound was elucidated to be sodium 3-acetonyl-TNB-1-sulfonate on the basis of the elemental analysis and NMR spectroscopy. The Janovsky reaction of Na-TNB-S seems to give a mixture of Id as the major complex and IId as the minor one.

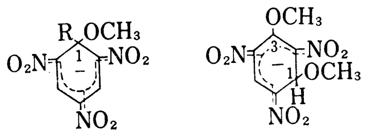
With respect to the Janovsky reaction it may be concluded that acetonate ions mainly attack the aromatic ring carbon carring no functional group and even if there is an effective leaving group on TNB moiety, only a part of the anions attacks the substituted position. This may be ascribed to that the standard Janovsky complex Ia is very stable in contrast to IVa and even if a substituted group at C-3 reduces the stability mainly through its sterical requirement, the complex(I) derived from substituted TNB still retains the high stability. It is very interesting to compare the Janovsky reaction with the trinitrophenylation of amino acid. In the reaction of amino acid with Na-TNB-S or PC, the substitution of the leaving group does occur.[10] And in the reaction of methoxide ion the substitution reaction occurs with ease, too.

For the comparison of the stability of the Janovsky compounds Ia, Ib and Ic with each others, the determination of the formation constant of the following equation is necessary.

$$\mathrm{III} + {}^{-}\mathrm{CH_2COCH_3} \rightleftharpoons \mathrm{I} \qquad (1)$$

$$K = \frac{[\mathrm{I}]}{[\mathrm{III}][{}^{-}\mathrm{CH_2COCH_3}]} \qquad (2)$$

It is difficult, however, to determine accurately the constant, for there are several equilibria other than equation 1 along the Janovsky reaction[1] and the atmospheric carbon dioxide interferes the concentration of alkali. But this difficulty can be avoided through the reaction in the co-existence of the TNB derivatives. In this method the formation constants can not be determined but the relative constants are obtainable as follows. The ratio of K of TNB to that of TNA is given by equation 3.



IVa : R=H
IVb : R=OCH$_3$

V

Chart 3

Table II. Extinction Coefficients of Ia and Ib

Wave length mμ	$\varepsilon^{\mathrm{Ia}}\times10^{-4}$	$\varepsilon^{\mathrm{Ib}}\times10^{-4}$
443	2.13	2.67
463	3.18	1.27
531	1.16	1.33
572	1.57	0.78

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[8] See the experimental section of the preceeding paper.[1]
[9] Condition: Wakogel B-5F, solvent benzene–methanol (3: 1).
[10] T. Okuyama and K. Satake, *J. Biochem.* (Tokyo), **47**, 454 (1960).

$$\frac{K_{\mathrm{TNB}}}{K_{\mathrm{TNA}}} = \frac{[\mathrm{TNA}][\mathrm{Ia}]}{[\mathrm{TNB}][\mathrm{Ib}]} \tag{3}$$

Stoichiometric concentrations of TNB and TNA are shown as follows.

$$[\mathrm{TNB}]_{\mathrm{st}} = [\mathrm{TNB}] + [\mathrm{Ia}] \tag{4}$$

$$[\mathrm{TNA}]_{\mathrm{st}} = [\mathrm{TNA}] + [\mathrm{Ib}] \tag{5}$$

The absorbance at a wave length λ in visible region is shown by equation 6.

$$E_{\lambda} = \varepsilon_{\lambda}^{\mathrm{Ia}}[\mathrm{Ia}] + \varepsilon_{\lambda}^{\mathrm{Ib}}[\mathrm{Ib}] \tag{6}$$

where the extinction coefficients of Ia and Ib at λ are given by $\varepsilon_{\lambda}^{\mathrm{Ia}}$ and $\varepsilon_{\lambda}^{\mathrm{Ib}}$, respectively. Although the wave lengths can be adopted arbitrarily, 443, 463, 531 and 572 mμ were selected in order to minimize the experimental error; the first and the third are the maximum wave lengths of Ib and the second and the last are those of Ia. Both TNB and TNA have negligible absorptions at those wave lengths. Extinction coefficients of Ia and Ib were estimated according to the procedure outlined previously[1)] and the results are given in Table II.

Sodium methoxide was added to the acetone solutions of TNB accompanied with TNA in various proportions and the solutions were kept at room temperature for about 48 hours until the reaction reached to equilibrium. An example of the absorption spectra measured is shown in Fig. 2. From the absorbance at the wave lengths cited above and the data shown in Table II the concentrations of TNB, TNA, Ia and Ib were calculated by using equations 4,5 and 6. From these concentrations the ratio of K_{TNB} to K_{TNA} was calculated by equation 3. These results are summerized in Table III. The proportion of K_{TNB} to K_{TNA} was calculated as 3.3.

TABLE III. Ratio of the Stability Constant of TNB to TNA

$[\mathrm{TNA}]_{\mathrm{st}}/[\mathrm{TNB}]_{\mathrm{st}}$	$[\mathrm{Ia}]\times10^5$ (M)	$[\mathrm{Ib}]\times10^5$ (M)	$[\mathrm{TNB}]\times10^4$ (M)	$[\mathrm{TNA}]\times10^4$ (M)	$K_{\mathrm{TNB}}/K_{\mathrm{TNA}}$
1	3.15	1.01	4.60	4.82	3.3
2	2.55	1.55	3.02	6.40	3.5
3	1.96	1.96	2.26	7.18	3.2
5	1.36	2.35	1.51	7.96	3.1
					mean 3.3

condition: $[\mathrm{TNB}]_{\mathrm{st}}+[\mathrm{TNA}]_{\mathrm{st}}=9.84\times10^{-4}$ M, $[\mathrm{OMe}^-]_{\mathrm{st}}=4.92\times10^{-5}$M
solvent system: acetone-methanol (98.4: 1.6, v/v)

In the same way K of PC might be determined but in this case picrate ion was formed as by-product. Equation 4 and the following equations were thus adopted for the calculation of K_{PC}.

$$\frac{K_{\mathrm{TNB}}}{K_{\mathrm{PC}}} = \frac{[\mathrm{PC}][\mathrm{Ia}]}{[\mathrm{TNB}][\mathrm{Ic}]} \tag{7}$$

$$E_{\lambda} = \varepsilon_{\lambda}^{\mathrm{Ia}}[\mathrm{Ia}] + \varepsilon_{\lambda}^{\mathrm{Ic}}[\mathrm{Ic}] + \varepsilon_{\lambda}^{\mathrm{picrate}}[\mathrm{picrate}] \tag{8}$$

$$[\mathrm{PC}]_{\mathrm{st}} = [\mathrm{PC}] + [\mathrm{Ic}] + [\mathrm{picrate}] \tag{9}$$

In this case the wave lengths were selected at 373, 450, 515 and 572 mμ. At 373 mμ picrate ion has a maximum and Ic has two maxima at 450 and 515 mμ. Extinction coefficients of Ic and picrate ion were obtained as shown in Table IV. One of the examples of the absorption spectra obtained is shown in Fig. 3. The calculated data of $K_{\mathrm{TNB}}/K_{\mathrm{PC}}$ in various proportions of the stoichiometric concentrations of TNB to those of PC are collected in Table V. From the data of Table III and Table V the proportion of K_{PC} to K_{TNA} was calculated as 2.1.

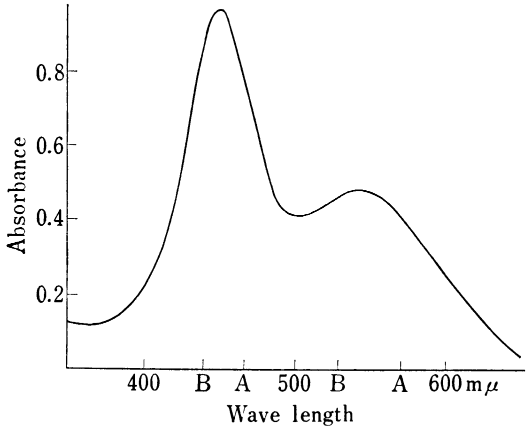

Fig. 2. Absorption Spectrum due to Janovsky Reaction of Mixture of TNB and TNA at Equilibrium Condition

A and B represent the wave lengths of absorption maxima of Ia and Ib, rspectively. $[TNA]_{st}/[TNB]_{st}=5$ Other conditions are given in Table III.

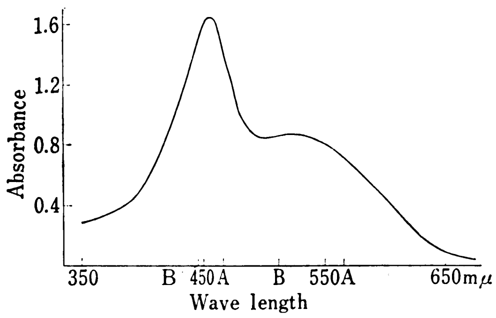

Fig. 3. Absorption Spectrum due to Janovsky Reaction of Mixture of TNB and PC at Equilibrium Condition

A and B represent the wave lengths of absorption maxima of Ia and Ic, respectively. $[TNB]_{st}/[PC]_{st}=4/7$ Other conditions are given in Table V.

TABLE IV. Extinction Coefficients of Ic and Picrate

Wave length mμ	$\varepsilon^{Ic}\times10^{-4}$	$\varepsilon^{picrate}\times10^{-4}$
373	1.82	1.82
450	2.78	0.37
515	1.97	0.00
572	0.86	0.00

TABLE V. Ratio of the Stability Constant of TNB to PC

$[TNB]_{st}/[PC]_{st}$	$[Ia]\times10^5$ (M)	$[Ic]\times10^5$ (M)	$[TNB]\times10^4$ (M)	$[PC]\times10^4$ (M)	$[picrate]\times10^5$ (M)	K_{TNB}/K_{PC}
5/6	3.09	2.09	3.79	4.60	1.07	1.8
4/7	2.35	2.47	3.05	5.38	1.16	1.7
3/8	1.78	3.11	2.28	6.12	1.20	1.5
2/9	1.15	3.48	1.52	6.91	1.20	1.5
						mean 1.6

condition: $[TNB]_{st}+[PC]_{st}=9.02\times10^{-4}$M, $[OMe^-]_{st}=9.84\times10^{-5}$M
solvent system: acetone-methanol (98.4: 1.6,v/v)

These results indicate that the substitution of Ia at C-3 position with chloro or methoxy group reduce its stability so slightly as Ib or Ic retains still fairly large one. In general the more the electron density in ring of Meisenheimer type compounds decreses, the more the compound is stable.[11] In trinitrophenetol two nitro groups in ortho position are significantly rotated out of the plane of the phenyl ring, one by 62° and another one by 33°.[12] So in the case of Ib or Ic the substituent at C-3 probably reduces the stability through the reduction

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11) H. Hosoya, S. Hosoya and S. Nagakura, *Theoret. Chim. Acta*, **12**, **117** (**1968**).

12) C.M. Gramaccioli, R. Destro and M. Simonetta, *Chem. Commun.*, **1967**, **331**.

of the resonance effect of the two nitro groups due to its sterical requirement and the third nitro group at C-6 must play a great role on the stability of the Janovsky compound. In the reaction of TNA with methoxide ion in dimethylsulfoxide, the addition at C-3 occurs at first giving V but it is not so stable to exist for a long time and finally only the stable Meisenheimer compound IVb are formed.[13] It may be reasonable that IIb or IIc is not formed owing to the large stability of Ib or Ic.

The stability of the various Meisenheimer type compounds of TNB having different substituents at the tetrahedral carbon atom will be reported in the near future in connection with their visible, infrared and NMR spectra.[14]

Experimental

Materials and Instruments——PC was prepared from picric acid according to Jackson's method[15] and was recrystalized from benzene–EtOH mixture, mp 83°. Na-TNB-S was commercial product ($C_6H_2(NO_2)_3$-$SO_3Na \cdot 2H_2O$). Other materials were described in the preceeding paper.[1] Instruments were shown also in the preceeding report.[1]

Treatment of the Janovsky Complex of PC with Acid and the Column Chromatography of the Products——Twenty milliliters of 2N NaOMe was added to 200 ml of acetone. After about a minute the solution was added to 5 g of PC in 2 liters of acetone. It was stirred for an hour and without isolation of the Janovsky complex 30 ml of 2N HCl was added dropwise for 20 min. After the mixture was stirred for 30 min, solvent was removed under reduced pressure. This procedure was repeated twice and 10.2 g of gummy substance was obtained. The product whose TL chromatogram is given in Fig. 4 was chromatographed on Wakogel-50 (50—200 mesh). PC (6.1 g) was developed by benzene and 3-acetonyl-PC (1.1 g) was obtained from 50% $CHCl_3$–benzene fraction. Oily substance (0.35 g) was eluted with 60% $CHCl_3$–benzene. This fraction was re-chromatographed on 15 g of Polyamide C-200 (Wako Pure Chemical Industries, Ltd.) and 144 mg of white needles, mp 97.5—98°, was obtained from 50% MeOH–H_2O which had the same *Rf* value and alkaline color on TL chromatogram as those of PA. This was identified with 3-acetonyl-4,6-dinitrochlorobenzene as described below.

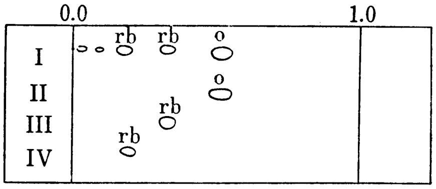

Fig. 4. Thin Layer Chromatogram of Products from Acidified Janovsky Reaction of PC

sample: I-gummy products, II-PC, III-3-acetonyl-PC, IV-PA
plate: Wako-gel B-5, solvent system: benzene-chloroform (2: 1), detector: 2N-NaOH, o=orange rb=reddish brown

Identification of 3-Acetonyl-4,6-dinitrochlorobenzene——Beilstein reaction was positive. IR ν_{max}^{KBr} cm^{-1}: 1719 (C=O), 1528 (asym NO_2). *Anal.* Calcd. for $C_9H_7O_5N_2Cl$: C, 41.78; H, 2.73; N, 10.83. Found: C, 41.75; H, 2.41; N, 10.17. NMR (in acetone-d_6) ppm[16]: 8.69 (1H, singlet, $C_{(5)}$-H), 7.80 (1H, singlet, $C_{(2)}$-H), 4.46 (2H, singlet, CH_2), 2.36 (3H, singlet, CH_3). mp 98° lit.[7] 97—98°.

Treatment of the Janovsky Complex of Na-TNB-S with Acid and the Column Chromatography of the Products——To 100 ml of acetone containing 176 mg of Na-TNB-S·$2H_2O$ 0.25 ml of 2N NaOMe was added. After 2 min it was acidified with 2N HCl and the solvent was removed under reduced pressure. PA was detected by TLC and GLC. Through polyamide column chromatography 5 mg of PA and 45 mg of sodium 3-acetonyl-TNB-1-sulfonate was obtained. *Anal.* Calcd. for $C_9H_6O_{10}N_3SNa$: C, 29.12; H, 1.63; N, 11.32; S, 8.64; Na, 6.19. Found: C, 29.83; H, 1.94; N, 11.48; S, 8.18; Na, 6.08. NMR (in D_2O) ppm[16]: 8.74 (1H, singlet, arom. -H), 3.83 (2H, singlet, CH_2), 2.38 (3H, singlet, CH_3).

GLC of TNB Derivatives——1.5% SE-30 on Shimalite-W (60—80 mesh, 3 mm×2 m) and 3% OV-17 on Gaschrom-Q (60—80 mesh, 3 mm×3 m) were used. Nitrogen carrier gas was used at 60 ml/min of flow rate. Both the detector and injection port temperatures were arranged at 250° and the column bath temperature was arranged at 140° in the case of SE-30 or at 210° in the case of OV-17.

Estimation of the Relative Stability Constants of Ia, Ib and Ic——To appropriate concentration of the mixture of TNB derivatives in 6 ml of acetone 0.1 ml of NaOMe was added. The number of moles of Na-

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[13] K.L. Servis, *J. Am. Chem. Soc.*, 89, 1508 (1967).
[14] A part was presented already at the 91st Annual Meeting of the Pharmaceutical Society of Japan, Apr. 1971.
[15] C.L. Jackson and F.H. Gazzole, *Am. Chem. J.*, 23, 384 (1900).
[16] Reference: tetramethylsilane.

OMe was selected to be smaller than that of the mixture of TNB derivatives. After the reaction reached to equilibrium (about 48 hr) the spectra were measured and the calculation was performed.

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