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The Syntheses of Several *N*,*N'*-Bis(hydroxymethyl)parabanic Acid Derivatives

Shigeo TANIMOTO,* Ryozo TANIYASU, and Masaya OKANO
Institute for Chemical Research, Kyoto University, Uji, Kyoto 611

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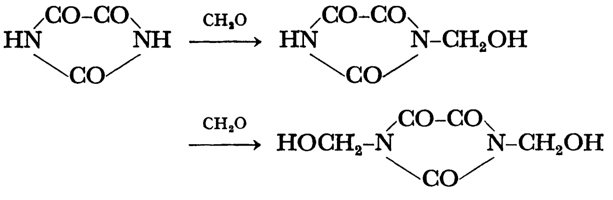
Synopsis. Starting from *N*,*N'*-bis(hydroxymethyl)parabanic acid, the following new compounds have been synthesized: *N*,*N'*-bis(arylaminomethyl)parabanic acids, *N*,*N'*-bis(bromomethyl)parabanic acid, and *N*,*N'*-bis(alkoxymethyl)parabanic acids.

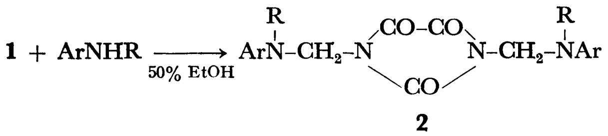
Though *N*,*N'*-bis(hydroxymethyl)parabanic acid (**1**) may serve as a reactive bifunctional heterocycle, little is known about its reactions or about its derivatives. The present communication will be concerned with the syntheses some of its derivatives.

The preparation of **1** from parabanic acid and two moles of formaldehyde was first reported by Oda and Baba:1)



1

When **1** was mixed with aromatic primary or secondary amines in 50% ethanol at room temperature, the corresponding bisarylaminomethyl compounds (**2**) were readily formed. They separated out from the reaction medium in good yields and were easily purified by recrystallization. Several bisarylaminomethyl compounds are listed in Table 1.



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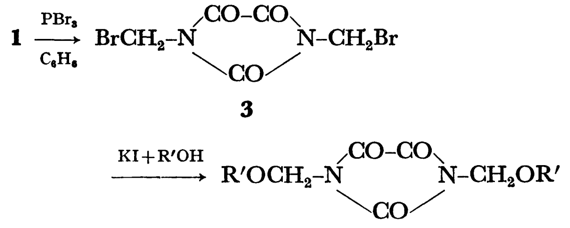
A similar transformation, proposed by Winstead and Heine2) as a method for the identification of aromatic amines, involves the condensation of phthalimide with formaldehyde and aromatic amines in boiling 80% ethanol. Since our reaction proceeds smoothly without heating, it may also offer advantages in the identification of primary or secondary aromatic amines as well as in their removal from the mixture with tertiary amines.

The conversion of **1** into *N*,*N'*-bis(bromomethyl)parabanic acid (**3**) was achieved by treatment with excess phosphorus tribromide in refluxing benzene. The bisbromomethyl compound thus obtained was considerably reactive toward nucleophiles. For example, when the reaction of **3** with primary or secondary aliphatic alcohols was carried out in the presence of potassium iodide, the expected *N*,*N'*-bis(alkoxymethyl)-



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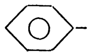
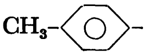
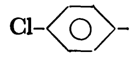
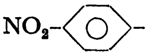
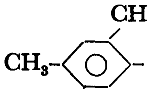
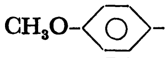
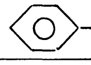
R' = Et, *n*-Pr, *iso*-Pr, *n*-Bu, *iso*-Bu

TABLE 1. PREPARATION OF *N*,*N'*-BIS(ARYLAMINOMETHYL)PARABANIC ACIDS

Ar	R	Method[a,b]	Yield[c] (%)	Mp (°C)	Found (%)			Calcd (%)		
					C	H	N	C	H	N
	H	A	73	71—74[d]	62.65	5.15	17.07	62.95	4.97	17.28
	H	B	99	134—137[d]	64.47	5.71	15.95	64.76	5.72	15.90
	H	B	93	68—72[e]	51.76	3.70	14.35	51.92	3.59	14.52
	H	B	76	231—234[d]	49.62	3.47	20.32	49.28	3.41	20.29
	H	A	70	60—64[d]	66.59	6.37	14.74	66.30	6.36	14.73
	H	B	89	69—73[d]	59.63	5.34	14.58	59.37	5.24	14.58
	CH_3	A	46	54—56[d]	64.72	5.82	15.87	64.76	5.72	15.90

a) Method A, amine dissolved in the same amount of 50% ethanol was added. b) Method B, amine dissolved in a minimum amount of 50% ethanol was added. c) Yields were based upon **1**, and referred to isolated ones. d) Recrystallized from ethanol. e) Recrystallized from benzene–*n*-hexane.

Table 2. Preparation of N,N'-bis(alkoxymethyl)parabanic acids

R′	Reaction temperature (time)	Yield (%)	Mp (°C)	Found (%)[a]			Calcd (%)		
				C	H	N	C	H	N
Me	Room temperature (2 hr)	Unidentified product of mp 195—198 °C							
Et	Room temperature (4 hr)	70	103—105[b]	46.82	6.19	12.17	46.95	6.13	12.17
n-Pr	Reflux (4—5 hr)	72	92—93[b]	51.00	6.99	10.82	51.15	7.03	10.85
iso-Pr	Reflux (5—6 hr)	45	86—88[b]	50.91	7.05	10.61	51.15	7.03	10.85
n-Bu	Reflux (4—5 hr)	78	75—77[b]	54.43	7.63	9.97	54.53	7.75	9.78
iso-Bu	Reflux (5—6 hr)	61	89—90.5[b]	54.66	8.01	9.64	54.53	7.75	9.78

a) Besides elemental analyses, the structure of the products was confirmed by NMR. b) Recrystallized from ligroin.

parabanic acids (**4**) were obtained in yields of 45—78%. However, the reaction with methanol failed to give the desired product. The results are shown in Table 2.

Experimental

N,N′-*Bis(hydroxymethyl)parabanic Acid (1).* A mixture of 5.7 g (0.05 mol) of parabanic acid and 8.0 g (0.10 mol) of 37% formalin was refluxed for 3—4 hr. The reaction mixture soon became a clear solution. When the solution was then allowed to cool, a crystalline solid separated. This was collected and dried to give 6.4 g (74%) of a white powder. Recrystallization from ethanol gave the pure compound; mp 127—131 °C (lit,[1] mp 130 °C).

N,N′-*Bis(arylaminomethyl)parabanic Acids (2).* A typical procedure will be described; all the other products were obtained in an analogous manner. A mixture of 1.4 g (0.015 mol) of aniline and the same amount of 50% ethanol was added, drop by drop, to a solution of 1.1 g (0.0063 mol) of **1** in 30 ml of 50% ethanol at room temperature. The solution immediately turned yellow, and a crystalline solid soon began to precipitate. After standing for 3—4 hr, the precipitate was collected and recrystallized from ethanol. Yield, 1.5 g (73%); mp 71—74 °C.

N,N′-*Bis(bromomethyl)parabanic Acid (3).* To a stirred suspension of 5.0 g (0.029 mol) of **1** and 200 ml of dry benzene, we added 30 g (0.11 mol) of phosphorus tribromide; the reaction mixture was then refluxed for 3 hr, during which time a vigorous reaction occurred. The filtration of the concomitant resinous product from the reaction mixture, followed by the removal of the solvent *in vacuo*, provided 3.9 g (45%) of a crude light-yellow solid. Recrystallization from benzene gave light-yellow crystals of **3**; mp 159—162 °C. Found: C, 20.35; H, 1.36; N, 9.36%. Calcd for $C_5H_4Br_2N_2O_3$: C, 20.02; H, 1.34; N, 9.34%. When stored in a moist atmosphere, **3** showed signs of decomposition, as evidenced by brown-coloring and a lowered melting point.

N,N′-*Bis(alkoxymethyl)parabanic Acids (4).* A typical example will be given. A solution of 1.5 g (0.005 mol) of **3** in 50 ml of ethanol containing 1.7 g (0.01 mol) of potassium iodide was stirred for 4 hr at room temperature. The subsequent evaporation of the ethanol gave white crystals of N,N'-bis(ethoxymethyl)parabanic acid (**4**, R′=Et); yield, 0.8 g (70%); mp 103—105 °C.

References

1) R. Oda and R. Baba, *Kogyo Kagaku Zasshi*, **64**, 741 (1961).

2) M. B. Winstead and H. W. Heine, *J. Amer. Chem. Soc.*, **77**, 1913 (1955).