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134. **Michiko Kagawa**: Anionotropic Rearrangement of Cyclic Ethynylcarbinol. II.[1] The Epimeric Resolution and the Mechanism of Anionotropic Rearrangement of Ethynylborneol.*[1]

(*Institute of Physical and Chemical Research**[2])

In the preceding paper[1] it was shown that 2-camphylideneacetaldehyde is prepared by the Meyer-Schuster rearrangement of 2-ethynylborneol with dilute hydrochloric acid and that 4-acetylborneol is prepared by the Rupe reaction with boiling in formic acid.

The present paper deals with the resolution of 2-ethynylborneol into two epimers and the behavior of these epimers on anionotropic rearrangement, together with the mechanism of the Meyer-Schuster and Rupe rearrangements of 2-ethynylborneol.

There are two processes commonly used for the preparation of 2-ethynylborneol, the essential difference being in the temperature at which camphor reacts with acetylene. Hurd and Christ[2] obtained 2-ethynylborneol (m.p. 93∼97°; yield, 13%) by reacting camphor with sodium and acetylene in boiling benzene.

Cuingnet[3] prepared the compound (m.p. 63°; yield, 65∼69%) by passing acetylene through a solution of sodiocamphor in liquid ammonia. Dulou obtained[4] the same compound (m.p. 85°; yield, 20%) and so did Sivkov and Matveeva[5] (m.p. 54∼56°).

Diverse melting points have thus been reported with no mention of the rotatory power. This divergence in the melting points was presumably due to the difference in the epimeric configuration of the compound as it was prepared by both the high- and low-temperature processes, which determined the production of either one or the other of the epimers.

As was described in the previous report, concerning the low-temperature process, sodiocamphor, when reacted with acetylene at 0° in benzene solution, yielded 2-ethynylborneol (m.p. 55°, $[\alpha]_D$ +17.7°; yield, 50%). A compound (yield 70%) of similar properties was obtained by a liquid ammonia method and this product was purified by alumina adsorption of the isomer in boiling hexane.

The high-temperature process was conducted as follows: Camphor was added to a suspension of sodium acetylide in benzene with boiling while passing acetylene through it. 2-Ethynylborneol (m.p. 85°, $[\alpha]_D$ ±0°∼3°; yield, 20%) was isolated as its silver salt. The product was purified by alumina adsorption in boiling hexane and elution of the

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*2 The nomenclature for camphor skeleton was used for ethynylcamphene and others as a matter of convenience.

1) Part I. M. Kagawa: This Bulletin, **7**, 306(1959).

2) C.D. Hurd, R.F. Christ: J. Am. Chem. Soc., **59**, 118(1937).

3) E. Cuingnet: Bull. soc. chim. France, **1955**, 91.

4) Dulou: Bull. inst. pin, **58**, 181(1934).

5) Sivkov, Matveeva: J. Gen. Chem. U.S.S.R., **14**, 319(1944)(C.A., **39**, 4066(1945)).

adsorbant with ether. The properties of the two 2-ethynylborneols were: m.p. 55°, $[\alpha]_{\mathrm{D}}$ +19.3°, from the low-temperature process and m.p. 87°, $[\alpha]_{\mathrm{D}}$ −14.0°, from the high-temperature process.

On usual treatment with 7% hydrochloric acid, each of the epimers of 2-ethynylborneol produced 2-camphylideneacetaldehyde and a small amount of a hydrocarbon.

Process	2-Camphanilideneacetaldehyde				2-Ethynylcamphene		
	Yield	b.p_5(°C)	$[\alpha]_{\mathrm{D}}$	semicarbazone m.p.(°C)	Yield	b.p_5(°C)	$[\alpha]_{\mathrm{D}}$
High-temp.	78%	92~102	−106.6°	223	8%	47~50	+7.0°
Low-temp.	50%	100~103	−120.0°	223	5%	40~50	+7.7°

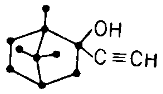
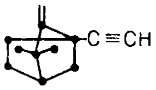
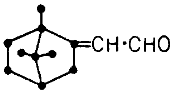
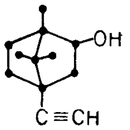
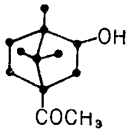
Again, on treatment with boiling formic acid, the epimers converted alike into 4-acetylborneol (b.$p_{3.5}$ 120°; semicarbazone, m.p. 203°), there being no difference in the products.

By hydrogenation of both 2-ethynylborneols, two 2-ethylborneols were obtained.

Process	b.p_5 (°C)	m.p.(°C)	$[\alpha]_{\mathrm{D}}$	
High-temp.	82~83	27	−19.3°	IR: 3583 cm^{-1} (OH)
Low-temp.	83	27	+ 2.5°	

These two epimers of 2-ethynylborneol, when treated with 7% or conc. hydrochloric acid, gave identical products, assumed to be 2-ethylidenecamphane (b.p_5 47°, $[\alpha]_{\mathrm{D}}$ −44.5°, n_{D}^{16} 1.4790, IR: 812 cm^{-1} ($^{\mathrm{C}}_{\mathrm{C}}\!\!>\!\mathrm{C{=}C}\!<\!^{\mathrm{C}}_{\mathrm{H}}$)). The structure of the compound was confirmed by

Table I. Anionotropic Rearrangement of 2-Ethynylborneol

 + acid	Temp. (°C)	(hr.)				
(1) 7% HCl	80	1	yield, 5.0% b.p_3 45~7° $[\alpha]_{\mathrm{D}}$ +6°	yield, 57.5% b.p_3 100° $[\alpha]_{\mathrm{D}}$ −120° Semi., 223°	—	—
(2) 30% HCl	70	1	—	yield, 89% b.p_4 111° $[\alpha]_{\mathrm{D}}$ −87.4° Semi., 223°	—	—
(3) 60% H_2SO_4	70	2	yield, 30% b.p_4 49~52° $[\alpha]_{\mathrm{D}}$ +10°	yield, 21% b.p_4 95~99° $[\alpha]_{\mathrm{D}}$ −187° Semi., 223°	—	—
(4) 90% HCOOH	40	48	trace	yield, 40% b.p_3 90~99° $[\alpha]_{\mathrm{D}}$ −120° Semi., 223°	—	—
(5) 20% HCOOH	100	10	yield, 53% b.p_5 52° $[\alpha]_{\mathrm{D}}$ +13.3°	trace	—	—
(6) 60% HCOOH	80	5	yield, 56% b.p_4 51° $[\alpha]_{\mathrm{D}}$ +6.8°	trace	—	—
(7) 90% HCOOH	60	48	yield, 24% b.$p_{3.5}$ 54~56°	trace	yield, 45.7% m.p. 122° $[\alpha]_{\mathrm{D}}$ +22°	—
(8) 90% HCOOH	100	6	—	trace	yield, 10% m.p. 122° $[\alpha]_{\mathrm{D}}$ +20°	yield, 67% b.p 135~140° Semi., 205°

its yielding camphor by oxidation with chromium trioxide. It was shown that the hydroxyl of 2-ethylborneol has a marked tendency to dehydrate against ethyl.

With a view to determining the mechanisms of the Meyer-Schuster rearrangement and the Rupe reaction, 2-ethynylborneol was treated at varying temperatures and varying concentrations of hydrochloric acid and formic acid.

When 2-ethynylborneol was submitted to rearrangement with hydrochloric acid or formic acid, an aldehyde or ketone was obtained. 2-Ethynylcamphene was always found to be formed and was inferred to be an intermediate substance of this reaction. Therefore, this hydrocarbon was treated with hydrochloric acid, and it gave 2-camphylideneacetaldehyde (b.p_6 110°, $[\alpha]_D$ −87.8°; yield, 47%. Semicarbazone, m.p. 223°). When treated with formic acid it yielded 4-ethynylborneol (m.p. 120°, $[\alpha]_D$ +22.06°; yield, 47%) and 4-acetylborneol (b.p_3 135∼140° : Semicarbazone, m.p. 205°).

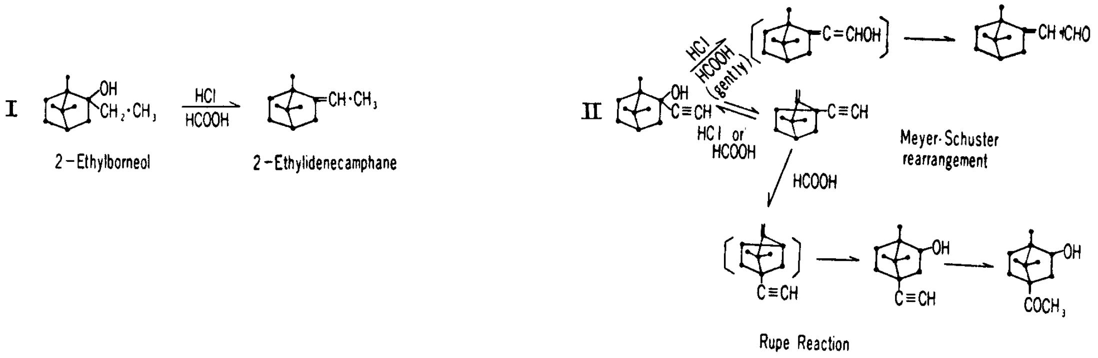


Chart 1.

As stated above, 2-ethylborneol yields 2-ethylidenecamphane on treatment with hydrochloric acid showing a greater tendency to exocyclic than to endocyclic dehydration, and 2-ethylcamphene is presumably formed from the latter. With 2-ethynylborneol, however, an endocyclic dehydrogenation occurs first to form 2-ethynylcamphene. In this case the Rupe reaction cannot proceed further in the presence of hydrochloric acid. At the same time a Meyer-Schuster rearrangement proceeds slowly and unsaturated aldehyde (2-camphylideneacetaldehyde) is formed by passing through allene alcohol. The former (endocyclic) dehydration is reversible; 2-ethynylborneol (from 2-ethynylcamphene) is regenerated and the main reaction proceeds as with unsaturated aldehyde. Then 2-camphylideneacetaldehyde is obtained, always accompanied, however, with a small amount of 2-ethynylcamphene.

In the case of using formic acid, 2-ethynylborneol yields, as with hydrochloric acid, 2-camphylideneacetaldehyde under mild condition such as conc. formic acid and at a low temperature. With dil. formic acid and at a high temperature it forms only 2-ethynylcamphene, no Nametkin or Meyer-Schuster rearrangement being observed. With conc. formic acid and at a high temperature 4-ethynylborneol is produced by the Wagner-Nametkin rearrangement through 2-ethylcamphene. Finally, 4-acetylborneol is formed through hydration of ethynyl by prolonged boiling. Although Hurd and Christ presumed 2-acetylcamphene as an intermediate to be rearranged first to 4-acetylcamphene and then to 4-acetylborneol, the present experiment shows that it proceeds as ethyl radical as far as 4-ethynylborneol and then is hydrated in the final stage to 4-acetylborneol.

It was expected that if 2-ethynylcamphene was hydrated to 2-acetylcamphene, this should be the legitimate product of a Rupe reaction of 2-ethynylborneol. A modification of the Rupe reaction therefore became the main reaction, the Meyer-Schuster rearrangement occurring in part, indicating a slight trace generally of attendant unsaturated aldehyde.

A detailed report will follow concerning the steric structure of the two 2-ethynylborneol isomers obtained under varying conditions of the ethynyl reactions of camphor.

Experimental

Preparation of 2-Ethynylborneol—(a) The low-temperature process: A solution of 200 g. of camphor in 200 cc. dehyd. benzene was added to a boiling mixture of 75 g. $NaNH_2$ dispersed in 800 cc. dehyd. benzene, and the mixture was refluxed for 15 hr. with stirring. The reaction mixture was cooled to 0° and acetylene was passed through for 15 hr. with stirring. After standing overnight, the solution was poured into ice water, the benzene layer was separated, washed with 5% H_2SO_4, dried over anhyd. Na_2SO_4, and the solvent evaporated. The crystalline residue was dissolved in MeOH and treated with ammoniacal $AgNO_3$ to form the silver salt. The silver salt was isolated, dried, and extracted with ether to remove camphor and resinous matter. The purified silver salt, weighing 180 g., was added to a solution of 100 g. NH_4Cl in 160 cc. H_2O and heated for 3 hr. The precipitated AgCl was filtered off and the filtrate was extracted with ether. The ether solution was dried over anhyd. Na_2SO_4, evaporated, and 47 g. of 2-ethynylborneol was obtained; m.p. 55°, $[\alpha]_D$ +17.7° (in EtOH, l=10 cm., c=20).

(b) By liquid-NH_3 method: To 250 cc. of liquid NH_3, 0.1 g. of finely powdered $Fe(NO_3)_2 \cdot H_2O$ and 8 g. of Na were added at −35° with stirring. After 1 hr., when the formation of $NaNH_2$ was completed, acetylene was passed through at −35° for 2 hr. to yield Na acetylide. A solution of 50 g. of camphor dissolved in 80 cc. of ether and toluene (1:1) was added to the solution of Na acetylide in liquid NH_3, acetylene being also passed through while cooling for 3 hr. After standing overnight, 100 cc. of a mixture of ether and toluene (1:1) was added to the reaction mixture and stirred for 3 hr. The reaction mixture was poured into water, the organic layer was washed with dil. H_2SO_4, dried over anhyd. Na_2SO_4, and the solvent was removed. The crystalline residue was purified by the Ag salt method to give 25 g. (50%) of 2-ethynylborneol, m.p. 55°, $[\alpha]_D$ +14.7° (in EtOH, l=10 cm., c=20).

Purification of 2-ethynylborneol by means of alumina: To a solution of 50 g. of 2-ethynylborneol ($[\alpha]_D$ +14~17°) in 1 L. of petr. ether 10 g. of alumina was added and refluxed for 2 hr. with stirring. The adsorbant was removed by filtration, fresh alumina was added again to the filtrate, and maintained at the boiling temperature. This method was repeated 3 times and 2-ethynylborneol (m.p. 55°, $[\alpha]_D$ +19.31°; 30% yield) was left in the filtrate.

(c) The high-temperature process: Through a boiling mixture of 13 g. of $NaNH_2$ dispersed in 150 cc. of dry toluene, acetylene was passed for 6 hr. with stirring. A solution of 25 g. of camphor dissolved in 50 cc. of toluene was added dropwise into the boiling mixture of Na-acetylide while passing through acetylene. The reaction mixture was treated by the usual method and the silver salt was isolated to give 7 g. (28%) of 2-ethynylborneol, m.p. 83~85°, $[\alpha]_D$ +3.6° (in EtOH, l=10 cm., c=20).

Purification of 2-ethynylborneol by alumina adsorption: 100 g. alumina was added to a solution of 90 g. of 2-ethynylborneol ($[\alpha]_D$ +3°) dissolved in 1800 cc. petr. ether and the mixture was refluxed for 2 hr. with stirring. The adsorbant was isolated by filtration and eluted with ether by using the Soxhlet apparatus to yield Fract. 1. The filtrate was again treated by the above method to isolate Fract. 2, and the process was repeated.

Fraction No.	Yield (g.)	Yield (%)	$[\alpha]_D$	m.p. (°C)
1	6	6.6	−7.37°	84~85
2	8	8.8	−7.76°	84~85
3	8	8.8	−6.86°	83
4	7	7.7	−1.47°	82
Filtrate	64	70	+7°	80

Fractions 1 and 2 were once more purified by the same method.

	Yield (g.)	$[\alpha]_D$	m.p. (°C)
Adsorbed fraction	2	−14.22°	87
Filtrate fraction	12	− 3.5°	85

Rearrangement of Epimer of 2-Ethynylborneol by HCl—Low-temperature process: To a mixture of 50 cc. of HCl and 120 cc. of H_2O, 20 g. of 2-ethynylborneol (m.p. 55°, $[\alpha]_D$ +18°) in 90 cc. *iso*-PrOH was added and the mixture was refluxed for 1 hr. with stirring. The reaction mixture was diluted with H_2O and extracted with ether. The organic layer was washed with H_2O, dried, and the solvent distilled off.

The oily residue was fractionated as follows:

(1) Indicated presence of $(\text{-C}\equiv\text{CH})$, b.p$_5$ 47～57°, 5%.

(2) 2-Camphylideneacetaldehyde, b.p$_5$ 90～103°, 57.5%, $[\alpha]_D$ −120°. Semicarbazone, m.p. 223°.

High-temperature process: A mixture of 10 g. of 2-ethynylborneol (m.p. 85°, $[\alpha]_D$ −5°) and 45 cc. of *iso*-PrOH, 25 cc. of HCl, and 56 cc. of H_2O was treated as above.

The oily residue was fractionated as follows:

(1) Indicated presence of $(\text{-C}\equiv\text{CH})$, b.p$_5$ 47～55°, 10%.

(2) 2-Camphylideneacetaldehyde, b.p$_5$ 103～104°, 50%. Semicarbazone, m.p. 223°.

Hydrogenation of 2-Ethynylborneol—Low-temperature process: A solution of 10 g. of 2-ethynylborneol (m.p. 55°, $[\alpha]_D$ +18°) in 90 cc. of MeOH was hydrogenated in the presence of 0.2 g. of Raney Ni at 4 atm. When H_2-uptake was completed, the mixture was filtered to remove the catalyst and the solvent was evaporated. Distillation of the residue yielded 9 g. of 2-ethylborneol, b.p$_5$ 83°, m.p. 27～28°, $[\alpha]_D^{16}$ +2.5°.

High-temperature process: 10 g. of 2-ethynylborneol (m.p. 85°, $[\alpha]_D$ −5°) was treated in the same way. Product: 2-Ethylborneol, b.p$_5$ 83°, m.p. 27°, $[\alpha]_D$ −19.3°.

Dehydration of 2-Ethylborneol—(1) With HCl: (a) Low-temperature process: A mixture of 5 g. 2-ethylborneol (b.p$_5$ 83°, m.p. 27～28°, $[\alpha]_D$ +2.5°), 5.5 cc. of *iso*-PrOH, 25 cc. of HCl, and 44.5 cc. of H_2O, was refluxed for 5 hr. with stirring. The reaction mixture was diluted with H_2O and extracted with ether. The ether solution was washed with H_2O and dil. Na_2CO_3 solution, dried over anhyd. Na_2SO_4, and the solvent was evaporated, affording 3 g. of 2-ethylidenecamphane, b.p$_5$ 45.5°, $[\alpha]_D$ −44.7°, n_D^{20} 1.4790.

(b) High-temperature process: 10 g. of 2-ethylborneol (b.p$_5$ 85°, m.p. 27°, $[\alpha]_D$ −19.3°) was treated as above. Product: 2-Ethylidenecamphane (b.p$_5$ 47～47.5°, $[\alpha]_D$ −44.5°, n_D^{16} 1.4800).

(2) With HCOOH: A mixture of 7 g. of 2-ethylborneol and 50 cc. of 90% HCOOH was refluxed for 2 hr. After the reaction mixture was diluted with H_2O and extracted with ether, the organic layer was washed with H_2O and dil. Na_2CO_3 solution, dried over anhyd. Na_2SO_4, and the solvent was removed to give 5 g. of oil, b.p$_{5.5}$ 52°, $[\alpha]_D$ −40°.

Both epimers yielded the same products.

Oxidation of 2-Ethylidenecamphane with CrO_3—A mixture of 3 g. of 2-ethylidenecamphane, 10 g. of CrO_3, and 30 cc. of H_2O was refluxed for 10 hr. The reaction mixture was extracted with ether, the organic layer was washed with H_2O and dil. Na_2CO_3 solution, dried over anhyd. Na_2SO_4, and the solvent was removed to give 1 g. of camphor, m.p. 175°.

Rearrangement of 2-Ethynylborneol—(1) With 30% HCl: A mixture of 8 g. of 2-ethynylborneol and 50 cc. of 30% HCl was warmed at 70° for 1 hr. with stirring. The reaction mixture was treated as usual. Distillation of the oil yielded 7.1 g.(39%) of 2-camphylideneacetaldehyde, b.p$_4$ 111°, $[\alpha]_D$ −87.4°. Semicarbazone, m.p. 223°.

(2) With 60% H_2SO_4: A mixture of 10 g. of the sample and 50 cc. of 60% H_2SO_4 was warmed at 70° for 2 hr. with stirring. The reaction mixture was diluted with H_2O and extracted with ether. The organic layer was washed with H_2O and dil. Na_2CO_3 solution, dried over anhyd. Na_2SO_4, and the solvent removed. Fractional distillation of the residue gave 2-ethynylcamphene, (3.0 g., 30%), b.p$_4$ 49～52°, $[\alpha]_D$ +10°; and 2-camphylideneacetaldehyde, b.p$_4$ 95～99° (2.1 g., 21%), $[\alpha]_D$ −187° (semicarbazone, m.p. 223°).

(3) With 90% HCOOH at 40°: A mixture of 7 g. of the sample and 42 cc. of 90% HCOOH was left standing at 40° for 2 days. The reaction mixture was diluted with H_2O and extracted with ether, which was washed with H_2O and dil. Na_2CO_3 solution, and oily residue was obtained from the organic layer. By distillation, 3 g. of 2-camphylideneacetaldehyde (b.p$_3$ 90～97°, $[\alpha]_D$ −120°; semicarbazone, m.p. 223°) was obtained.

(4) With 20% HCOOH: A mixture of 8 g. of the sample and 80 cc. of 20% HCOOH was boiled for 10 hr. The reaction mixture was treated as usual. Distillation of the residue yielded 2-ethynylcamphene, b.p$_5$ 52°, $[\alpha]_D$ +13.3°; 4.3 g. (yield, 55%).

(5) With 60% HCOOH: A mixture of 8 g. of the sample and 50 cc. of 60% HCOOH was warmed at 80° for 5 hr. The reaction mixture was diluted with H_2O and extracted with ether. The organic layer was washed with dil. Na_2CO_3 solution, dried over anhyd. Na_2SO_4, and evaporated. By distillation, 2-ethynylcamphene (b.p$_4$ 51°, $[\alpha]_D$ +6.8°) was obtained. Yield, 4.5 g.(56%).

(6) With 90% HCOOH: A mixture of 10 g. of 2-ethynylborneol and 60 cc. of 90% HCOOH was warmed at 60° for 48 hr. The reaction mixture was treated as usual and the fractional distillation of the residue gave 2-ethynylcamphene, b.p$_{3.5}$ 54～56° (1.7 g., 24%), a fraction of b.p$_{3.5}$ 100～101° (3.2 g.,

45.7%). This latter fraction was saponified with ethanolic KOH and 4-ethynylborneol (m.p. 122°, $[\alpha]_D$ $+22°$(in EtOH, $l=10$ cm., $c=20$)) was obtained.

(7) With 90% HCOOH : A mixture of 10 g. of the sample and 60 cc. of 90% HCOOH was refluxed at 100° for 6 hr. and the reaction mixture treated as usual. The fractional distillation gave a fraction of b.p$_{2.5}$ 100~101°, which was saponified with ethanolic KOH to yield 4-ethynylborneol, m.p. 120°, $[\alpha]_D$ $+20°$(1 g.; yield, 10%); and a fraction of b.p$_{3.5}$ 110~113°, which was saponified with ethanolic KOH to yield 4-acetylborneol, b.p$_{3.5}$ 130~135° (6.7 g., yield, 67%); semicarbazone, m.p. 205°.

Summary

1) The epimers of 2-ethynylborneol were resolved by means of alumina adsorption. They behaved similarly to an anionotropic rearrangement, forming the same product.

2) 2-Ethylborneol was dehydrated in exocyclic way with hydrochloric acid or formic acid to form 2-ethylidenecamphane. 2-Ethylcamphene, which is presumably formed by endocyclic dehydration, was not found.

3) 2-Ethynylborneol yielded aldehyde or ketone by the action of hydrochloric acid or formic acid, respectively. These reactions were studied under varying conditions in order to determine the mechanisms of the rearrangement.

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135. Kyoji Hayano and Sataro Imado : Studies on Aluminum Complex Compound of PAS. I. Synthesis of Alumino-*p*-aminosalicylic Acid*[2] and its Calcium Salt.*[3]

(*Osaka Research Laboratory, Tanabe Seiyaku Co., Ltd.**[1])

The rôle of *p*-aminosalicylic acid (hereinafter abbreviated as PAS) as a chemotherapeutic is of value but PAS preparations now in use, such as PAS, PAS-sodium, and basic PAS-calcium, have many defects. PAS itself has an acid taste, PAS-sodium is bitter, and both have unpleasant taste on taking. Further, they are liable to cause gastrointestinal disturbances such as loss of appetite, vomiting, and diarrhoea. Therefore, basic PAS-calcium is more increasingly used than PAS-sodium at present, but even this is not tasteless and gastrointestinal disturbance is not rare. Improvement of PAS preparations to remove such defects has long been desired.

Recently, Deeb and others[1)] reported that a preparation of PAS utilizing buffer action of aluminum hydroxide gives very little gastrointestinal disturbance and maintains effective blood level over a long period. Based on this idea, a new compound in which aluminum is bonded to PAS was prepared in order to improve the foregoing defects in PAS preparations, whicn is described herein.

1. Alumino-*p*-aminosalicylic Acid (Al-PAS)

Past literature on a compound of PAS and aluminum is found only in the report of

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*[1] Kashima-cho, Higashiyodogawa-ku, Osaka (早野恭二, 今戸佐太郎).

*[2] Chemical term : Bis(*p*-aminosalicylato)aquahydroxoaluminatic acid trihydrate or heptahydrate. Abbreviated here as Al-PAS.

*[3] Chemical term : Calcium bis(*p*-aminosalicylato)aquahydroxoaluminate heptahydrate. Abbreviated here as Al-PAS-Ca.

1) E.N. Deeb, G.R. Vitagliano : Am. Rev. Tuberc., **72**, 543(1955).