THE PHARMACOLOGY OF SOME CYCLOHEXANOL DERIVATIVES

By M. Sirsi and P. Suryanarayana Murthy
(*Pharmacology Laboratory, Indian Institute of Science, Bangalore-3*)

Received August 11, 1955

Summary

Besides ethanol, the tertiary amyl alcohol (2-methyl-2-butanol) is the only simple alcohol which has found practical use as an hypnotic. The recent studies on the simple highly unsaturated carbinols as hypnotics has activated the interest for a systematic study of these groups of compounds as therapeutic agents.

Evaluation of the hypnotic and anæsthetic activities of a group of cyclohexanol derivatives, and a study of the toxicity and pharmacodynamic action of few of the active ones has revealed that some of these compounds produce rapid hypnosis and anæsthesia of short duration.

Of the substances tested, 2-methyl-1-ethinyl cyclohexanol was the least toxic with a chemo-therapeutic ratio of more than 5.

These preliminary studies indicate the possibility of obtaining rapid hypnotic and short acting anæsthetics in these cyclohexanol derivatives.

Although the physiological action of ethyl alcohol in producing sleep had been known since a very long time, it was only in the latter part of the 19th century that the systematic study of the alcohols as a class was carried out. All the aliphatic alcohols so far examined possess hypnotic properties and it was recognised as early as 1869[1] that the action becomes more pronounced with increasing molecular weight. It was also established that unsaturation in the molecule enhanced hypnotic effect. Besides ethanol, tertiary amyl alcohol—2-methyl-2-butanol—is the only, simple alcohol which has found practical use[2] and this was introduced around 1890 as Amylene hydrate. The recent studies on the simple highly unsaturated carbinols as hypnotics[3a, 3b] has activated the interest for a systematic study of these groups of compounds as therapeutic agents.

The studies here reported were undertaken to evaluate in a preliminary way, the hypnotic and anæsthetic activity of a group of Cyclohexanol derivatives synthesised specifically for this purpose, by Mr. M. C. Chaco and Dr. B. H. Iyer of the Organic Chemistry Department, Indian Institute of Science, Bangalore.

The rat has been generally regarded as the most suitable animal for such studies. For regularity of absorption intraperitoneal route was preferred.

Fitch and Tatum[4] have suggested that the intraperitoneal route closely approximates slow intravenous injection.

Healthy adult albino rats raised in our animal colony and weighing between 100–200 gm. were used in all the experiments. Minimum of seven days interval was given before the animals were used for re-testing. This time was found sufficient to prevent any cumulative effect. A group of five rats was used for each drug.

The definition of anæsthesia and hypnosis varies considerably in literature. Hypnosis, in our experiments, is defined as that condition in which it is not possible to elicit ' body righting reflexes ' and the animal remains in the position in which it is placed, but responds to pinching of the tail by body movements. The time from the moment of injection till this state is attained is termed the Induction time. The duration of activity is the interval from the start of hypnosis to signs of recovery. Anæsthesia is said to have developed if the animal fails to react to mechanical stimulation of the tail.

Rats were closely observed for sleep during the first three hours after injection; the time of onset and duration of hypnosis were recorded. Drugs were considered inactive if no hypnosis was observed within these three hours.

Preliminary trials with the cyclohexanol derivatives indicated that in doses up to 200 mg./kg. no hypnotic action was evident. At 220 mg./kg. some of the compounds exhibited hypnotic and anæsthetic effect. The results of the screening tests are shown in Table I and the detailed sequence of events is recorded in Table II.

TABLE I

*Hypnotic and anæsthetic activity of some cyclohexanol derivatives**

Dose: 220 mg./kg. Route: Intraperitoneal

Compound No.	Name of Compound	B.p./m.p.	Hypnotic and anæsthetic action
1	1-Ethinyl cyclohexanol ..	86–90°/26 mm.	+
2	2-Methyl-1-ethinyl cyclohexanol (solid form)	m.p. 60°	+
3	Do. (liquid form)	84·5°/17·5 mm.	+
4	3-Methyl-1-ethinyl cyclohexanol (solid form)	m.p. 23–25°	+
5	Do. (liquid form)	82°/10 mm.	+
6	4-Methyl-1-ethinyl cyclohexanol (solid form)	m.p. 43°	+
7	Do. (liquid form)	84°/10 mm. m.p. 43°	±
8	1-Vinyl cyclohexanol ..	73–77°/24 mm.	—

TABLE I—(*Contd.*)

Compound No.	Chemical formula	B.p./m p.	Hypnotic ond anæsthetic action
9	2-Methyl-1-vinyl cyclohexanol (from liq. 2-Me-1-ethinyl cyclohexanol)	72–74°/11·5 mm.	—
10	1-Ethyl cyclohexanol ..	81·5°/22 mm.	—
11	2-Methyl-1-ethyl cyclohexanol (from solid 2-Me-1-ethinyl cyclohexanol)	94°/23 mm.	—
12	2-Methyl-1-ethyl cyclohexanol (from liq. 2-Me-1-ethinyl cyclohexanol)	81–84°/23 mm.	—
13	3-Methyl-1-ethyl cyclohexanol (from liq. 3-Me-1-ethinyl cyclohexanol)	83–85°/15 mm.	—
14	2-Methyl-1-vinyl cyclohexanol (from solid 2-Me-1-ethinyl carbinol)	49°/0·5–1 mm.	—
15	3-Methyl-1-vinyl cyclohexanol (from solid 3-Me-1-ethinyl carbinol)	51°/0·5–1 mm.	—
16	3-Methyl-1-vinyl cyclohexanol (from liq. 3-Me-1-ethinyl carbinol)	66°/3·5 mm.	—
17	3-Methyl-1-ethyl cyclohexanol (from solid 3-Me-1-ethinyl carbinol)	66°/3·5 mm.	—
18	4-Methyl-1-vinyl cyclohexanol (from solid 4-Me-1-ethinyl carbinol)	50°/1·2 mm.	—
19	4-Methyl-1-vinyl cyclohexanol (from liq. 4-Me-1-ethinyl carbinol)	49°/0·5–1 mm.	—
20	4-Methyl-1-ethyl cyclohexanol (from solid 4-Me-1-ethinyl carbinol)	50°/0·5–1 mm.	—
21	4-Methyl-1-ethyl cyclohexanol (from liq. 4-Me-1-ethinyl carbinol)	53°/1·5–2 mm.	—
Kemithal sodium (220 mg./kg.)	Sodium cyclohexenyl-allyl thio-barbiturate		+
Phenobarbi-tone sodium (110 mg./kg.)	Sodium-5-phenyl-5-ethyl barbituric acid		+

Legend: + = hypnosis and anæsthesia present. ± = Slight hypnosis and no anæsthesia.
— = No hypnotic and anæsthetic action.

* Chemical data supplied by Chaco and Iyer.

TABLE II

Detailed analysis of the effect of Cyclohexanol derivatives exhibiting hypnotic activity

Dose: 220 mg./kg. Route: Intraperitoneal

The number of the compounds refer to the compounds shown in Table I.

Compound No.	Pre-hypnotic symptom	Time of onset of hypnosis	Duration (in minutes)	Anæsthesia
1	Nil	Immediate	25–60	+
2	Ataxia in few animals (2)	Immediate (3) 5–7 mins. (2)	20–30	+
3	Ataxia (2)	5–10 mins. (2) Immediate (3)	25–35	+
4	Ataxia (3)	5 mins. (3) Immediate (2)	25–40	+
5	Ataxia (3)	Partial hypnosis (3) Immediate (1) No hypnosis (1)	15–20	±
6	Excitement (2)	5 mins. (2) Immediate (3)	40–65 15–35	
7	Ataxia (5)	No hypnosis	..	
8 9 10 11 12 13	Slight ataxia in a few animals in each group	No hypnosis		
Kemithal sodium (Sodium cyclohexenyl-allyl thiobarbiturate)	Ataxia (2)	Immediate (3)	3–12 hrs. dozed condition, recovery complete after 16 hrs.	+

Five rats were used to test each compound.

The figures in bracket indicate the number of animals.

TABLE III

Acute toxicity of some cyclohexanol derivatives

Compound	No. of animals tested	Dose	Route	Mortality
2	5	1·1 g./kg.	I.P.	Nil
5	5	,,	,,	3
6	5	,,	,,	3

Toxicity studies

The acute toxicity of compounds 2, 5 and 6, which were available in quantity, were tried in doses upto 1·1 g./kg., which was five times the hypnotic dose. At this dosage level, the following results were observed:

This limited study indicates that compound No. 2 exhibits a chemotherapeutic ratio of more than 5. The active compounds produce rapid hypnosis and anæsthesia of short duration and hence could be of use in emergency anæsthesias.

Pharmaco dynamic studies

Some pharmaco dynamic effects of compounds 2, 3, 4, 5 and 6 which had shown hypnotic activity have been investigated.

The influence of the compounds when given by intravenous route on the blood pressure and respiration on dogs under seconal sodium anæsthesia is shown in Figs. 1, 2 and 3. The effect of the drugs on the parasympathetic and the sympathetic systems was studied at the same time, by noting the effect of the drug on the blood pressure changes induced by vagal stimulation, acetylcholine and adrenaline injection before and after the administration of the drugs. The vagal stimulation was through shielded electrodes from an induction coil, the peripheral vagal end being stimulated for 5 seconds. Acetylcholine and adrenaline doses used were 2 γ/kg. i.v.

50 mg. and 100 mg. of compound No. 2 did not cause any fall in blood pressure nor affect the respiration; the vagal, acetylcholine and adrenaline effects were undisturbed (Fig. 1). Drugs 3 and 4 in the dosage (100 mgs./kg.) caused fall in blood pressure and diminished respiratory movements. They did not exhibit any synergistic or antagonistic effect to vagal stimulation, acetylcholine and adrenaline injection (Fig. 2).

Substances 5 and 6 were intermediary in effect. A very slight fall in blood pressure was the only effect observed (Fig. 3).

The studies on the isolated guinea pig ileum reveals that the compounds 2, 5 and 6 in high concentrations possess spasmolytic action on acetylcholine and histamine induced spasms. In lower concentrations No. 2 showed slight anti-histaminic action only, while at this same dosage drugs Nos. 5 and 6 showed both anti-acetylcholine and anti-histaminic actions (Fig. 4 *a*, *b*, *c*, *d*).

Many hypnotics produce marked pharmacological effects. Avertin (Tribromethanol) produces a serious fall in blood pressure and depression of respiration which may be fatal. In ordinary doses it causes considerable fall of blood pressure, usually of short duration.[5]

In the case of the barbiturates it has been noticed that no definite relationship exists between the hypnotic efficiency and other pharmacological properties. Wide variations are noticed as regards vaso-depressor action, autonomic ganglion

blocking property, parasympatholytic and adrenolytic effects and bronchial resistance.[6–8] Absence of anti-spasmodic effect on isolated organs and no depression on respiration, in marked contrast to the barbiturates, has been reported for a few unsaturated carbinols which have exhibited significant hypnotic activity in several species.[9]

Of the substances tested in our series, 2-methyl-1-ethinyl cyclohexanol (Compound No. 2) exhibits no acute toxicity even at five times the hypnotic dose, while with compounds 5 and 6, more than 50% mortality was noticed at this level. The hypnosis produced was almost immediate, with majority of the active compounds and the anæsthesia induced was of short duration, lasting for about half an hour at this dosage. The anæsthesia was deep enough for minor operative procedures to be undertaken and the recovery phase was quick with no untoward symptoms. The pharmacodynamic actions on compound No. 2 show no effect on blood pressure or respiration.

These preliminary studies indicate the possibility of obtaining rapid hypnotic and short acting anæsthetics in these group of compounds.

The detailed chemistry of these synthetic compounds and the structure-activity relationship will be discussed in a separate communication by Chaco and Iyer.

Our thanks are due to Prof. D. K. Banerjee for his kind interest in the work and to Dr. K. P. Menon for advice and guidance.

References

1. Richardson .. *Med. Times and Gaz.*, 1869, **18**, 703.
2. Burger, A. .. *Medicinal Chemistry*, Interscience Publishers, New York, 1951. p. 129.
3. (*a*) Papa, D., Villani, F. J. and Ginsburg, H. F. *Archiv Biochem. Biophys.*, 1951, **33**, 482.
   (*b*) ———— .. *J. Am. Chem. Soc.*, 1954, **76**, 4446.
4. Fitch, R. H. and Tatum, A. L. *J. Pharmacol.*, 1932, **44**, 325.
5. Sollmann, J. .. *A Manual of Pharmacology*, W. B. Saunders & Co., 1942, p. 771.
6. Nickerson, M. and Goodman, L. S. *J. Pharmacol.*, 1947, **89**, 167.
7. Hunt, C. C. .. *Ibid.*, 1949, **95**, 177.
8. Sandberg, F. .. *Acta Physio Scandinavica*, 1952, **25**, supp. 91.
9. Margolin, S., Pertman, P., Villani, F. and Mc Gavack, T. H. *Science*, 1951, **114**, 384.

EXPLANATION OF FIGURES

FIG. 1. Dog, Seconal sodium anæsthesia. Record of systemic blood pressure (carotid artery) and respiration. Time interval equals to 6 secs. The effect of vagal stimulation (V), acetylcholine 2 γ/kg. (Ac) and adrenaline 2 γ/kg. (Ad) administration.

2 and 2′ indicate respectively the intravenous injection of 50 mg. and 100 mg. of compound 2. No diminution of response observed.

FIG. 2. Compound No. 3, 100 mg. given i.v. at 3. A fall in blood pressure and diminished amplitude of respiration observed. Other responses normal.

Compound No. 4. 100 mgms. i.v. at 4. Fall in blood pressure and diminished respiratory movements. Vagal and Ach. responses not interfered.

FIG. 3. At 5 and 6, compounds No. 5 and No. 6 given i.v., dose: 100 mg. A slight transient fall in blood pressure observed.

FIG. 4 (*a*, *b*, *c* and *d*). Spasmolytic effect of the various hypnotic drugs on the spasms induced by acetylcholine chloride (1 γ) and histamine dihydrochloride (1 γ) as tested on guinea pig ileum; Bath fluid: Magnesium free Tyrode solution (30 ml.); Temperature 35° C. ($\pm 0{\cdot}5°$). At the positions indicated by arrows the drugs are injected into the bath; while at the dots a wash is given. Ac., indicates acetylcholine; H., histamine; 2 *a*, 5 *a* and 6 *a*,—0·5 mg. of compounds 2, 5 and 6; 2 *b*, 5 *b* and 6 *b*—5·0 mg. of compounds 2, 5 and 6; 5·0 mg. of compound 8 is given at 8.

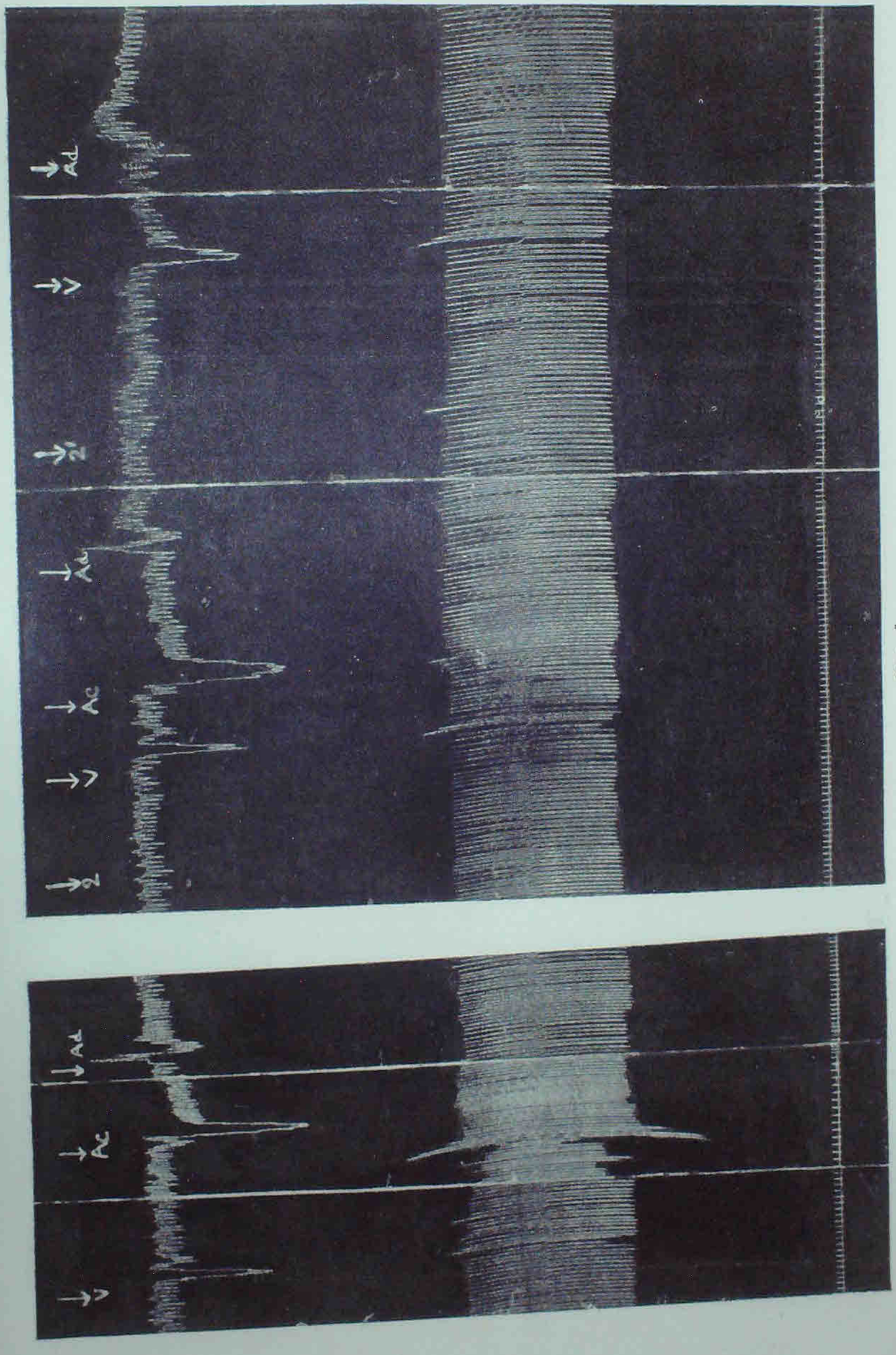

FIG. 1

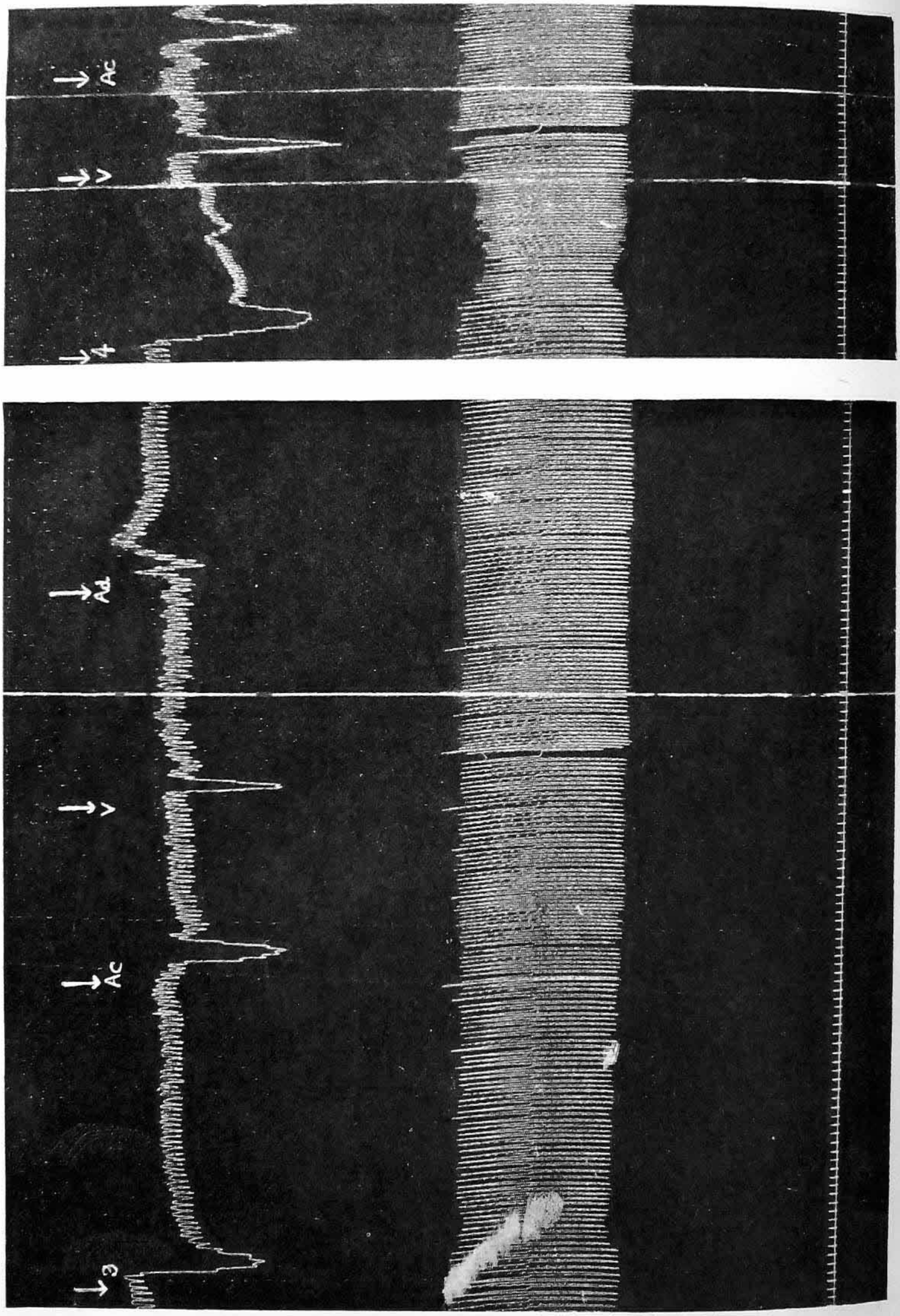

FIG. 2

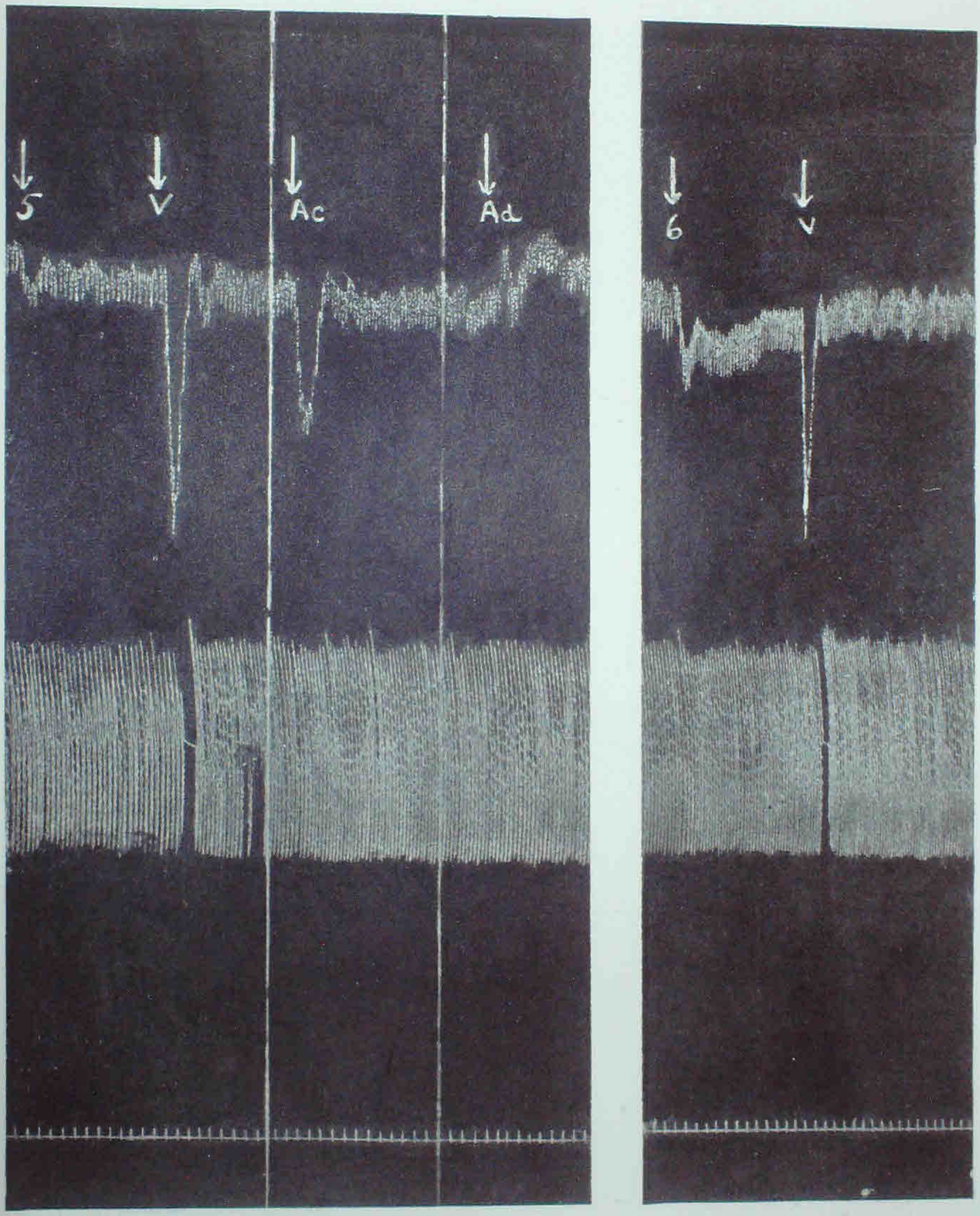

FIG. 3

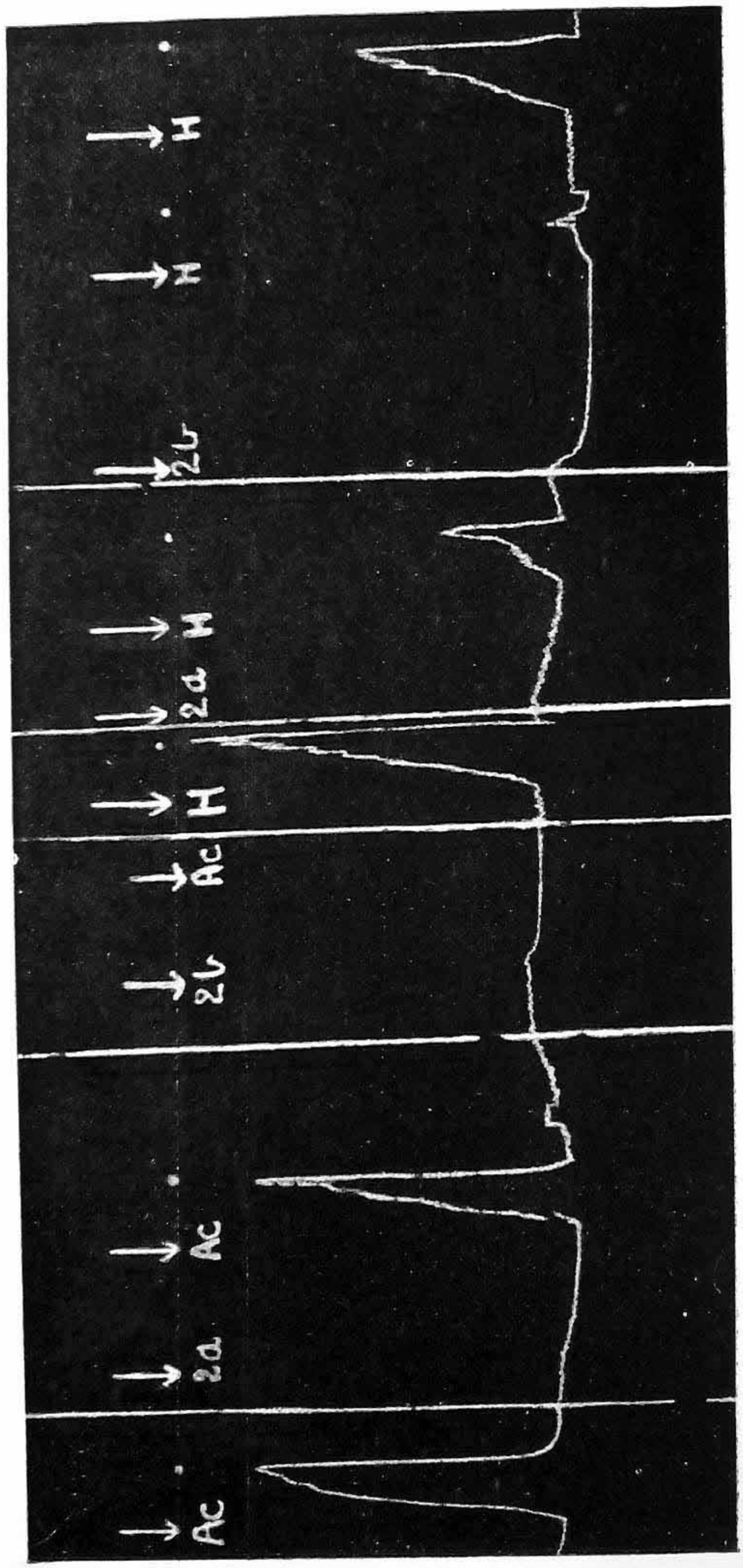

FIG. 4 (*a*)

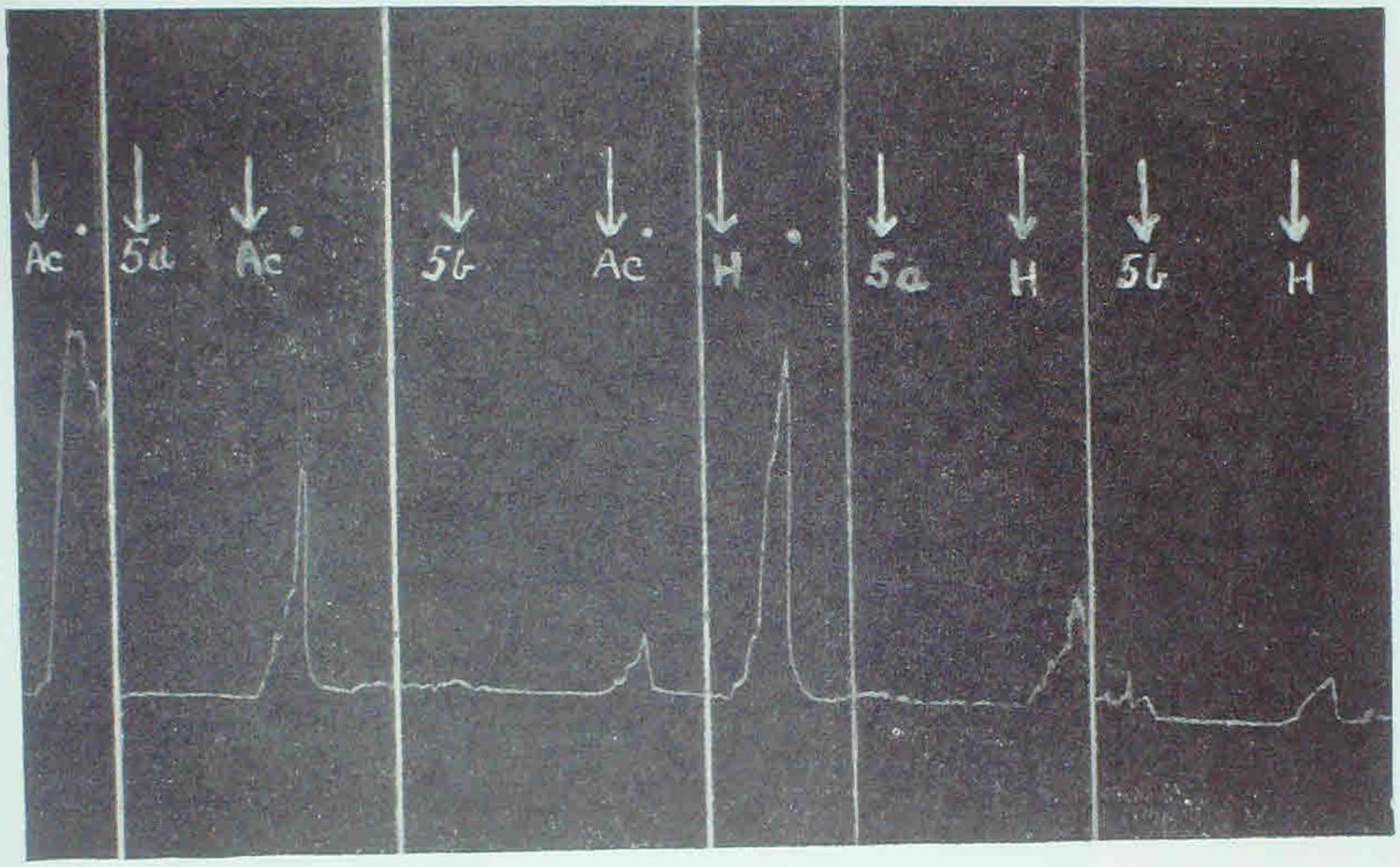

FIG. 4 (*b*)

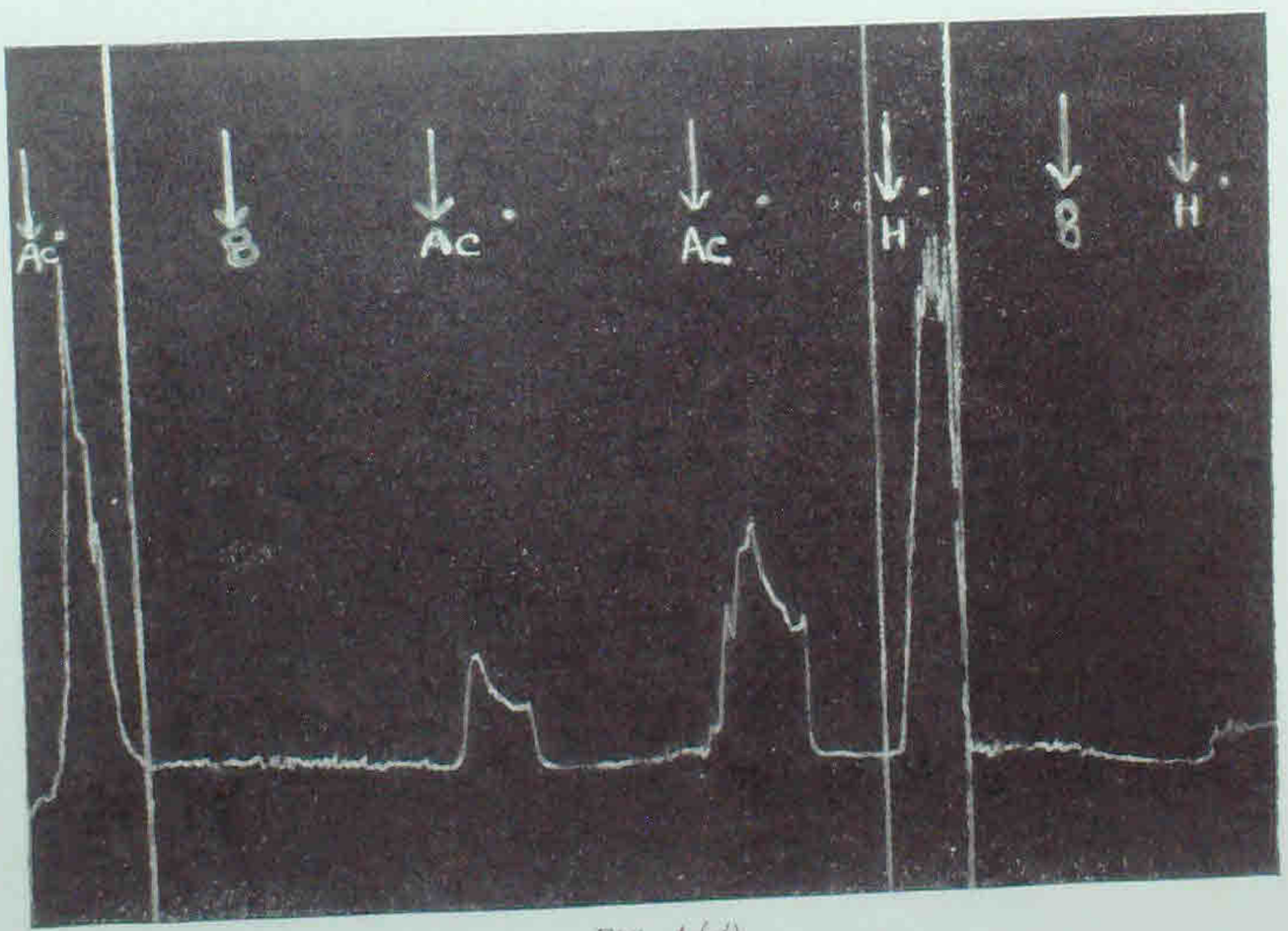

FIG. 4 (*d*)

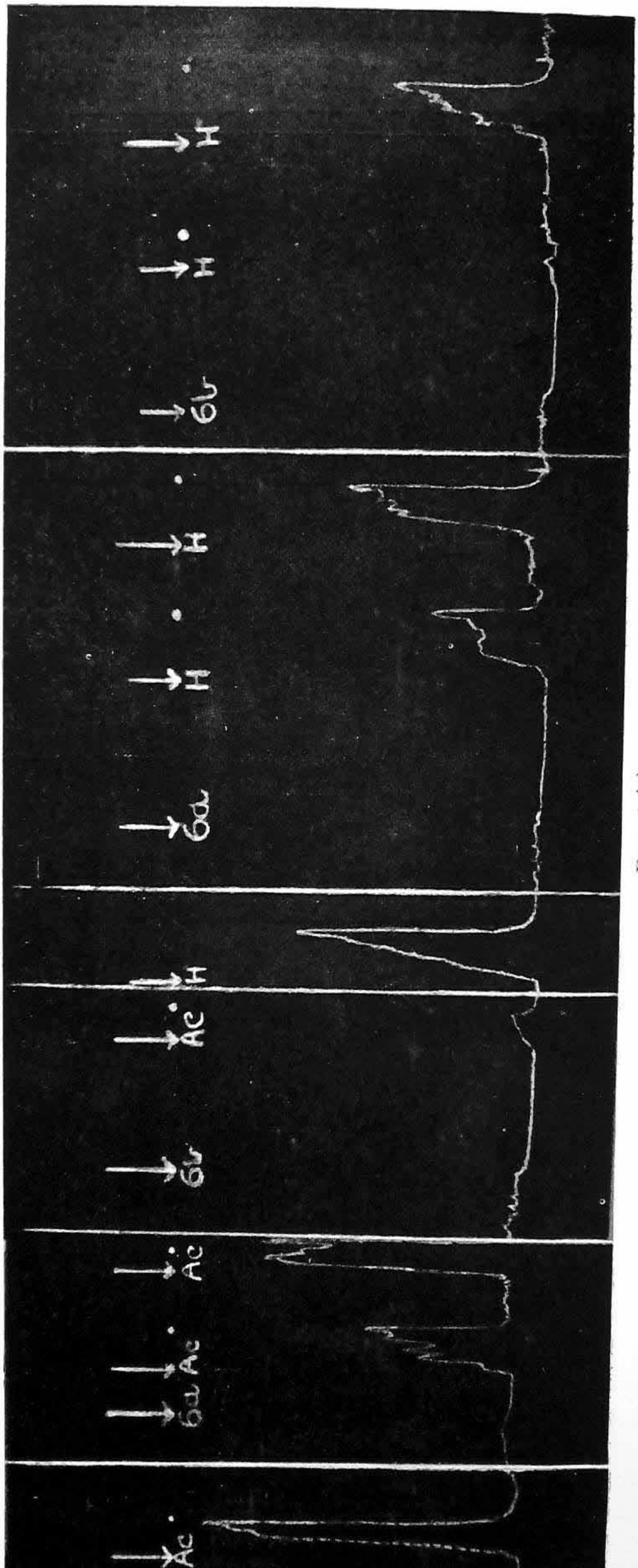

FIG. 4 (c)