The reaction between methylamine and yttrium chloride was studied by the method of isobaric thermal decomposition curves. This method consisted of the formation of the higher methylamine complex at 0°C, after which the complex was subjected to thermal decomposition at a constant pressure. The apparatus used has been previously described (*2*). The anhydrous yttrium chloride was prepared by heating the hexahydrate in a hydrogen chloride atmosphere with the following temperature stops: 4 hr at 90°C, 1 hr at 180°C, and 2 hr at 400°C (*3*). The resulting product was analyzed and found to be free of water. The preparation and purification of the methylamine has been described by Kenner and Felsing (*4*).

The thermal decomposition curve is shown in Fig. 1. According to the phase rule, a reversible phase that is stable over a specific temperature range can be considered a chemical compound. The curve was reproducible and reversible within an experimental error of ±0.5 percent. Four compounds can be identified from the curve: $Y(CH_3NH_2)_4Cl_3$, $Y(CH_3NH_2)_3Cl_3$, $Y(CH_2NH_2)_2Cl_3$, and $Y(CH_3NH_2)Cl_3$. The decomposition temperatures are given in Table 1.

It is interesting to note that a complex with five methylamine molecules was not found, as was the case with the rare-earth complexes. Even at 0°C, this complex could not be detected. It is obvious that the yttrium chloride complexes are less stable. According to ionic radii considerations, the smaller ion should form the more stable complex; therefore, the yttrium ion (1.06 A), being smaller than the rare-earth ions that were studied (122 to 1.11 A), should be more stable. Apparently other factors that make the influence of the smaller ion size of lesser importance must be present.

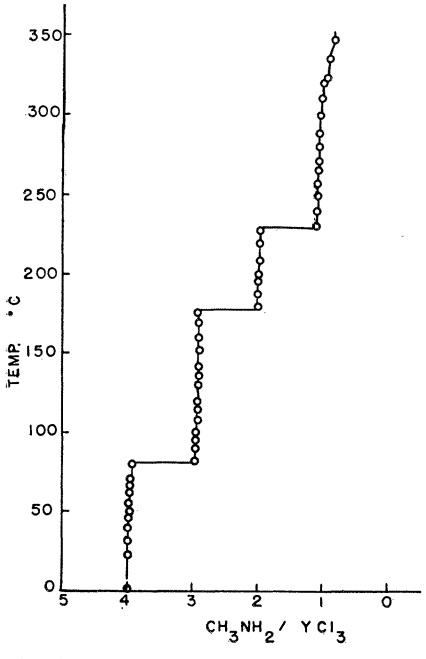

Fig. 1. The system of methylamine with yttrium chloride; pressure, 700 mm.

Table 1. Decomposition temperatures of the methylamine complexes of yttrium chloride

Transition	Temperature (°C)
$Y(CH_3NH_2)_4Cl_3 \rightarrow Y(CH_3NH_2)_3Cl_3 + CH_3NH_2$	82
$Y(CH_3NH_2)_3Cl_3 \rightarrow Y(CH_3NH_2)_2Cl_3 + CH_3NH_2$	180
$Y(CH_3NH_2)_2Cl_3 \rightarrow Y(CH_3NH_2)Cl_3 + CH_3NH_2$	232
$Y(CH_3NH_2)Cl_3 \rightarrow YCl_3 + CH_3NH_2$	> 360

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7 March 1955

Frenquel Corrects Certain Cerebral Electrographic Changes

Lysergic acid diethylamide (LSD-25), an alkaloid derived from ergot, produces in human subjects mental disturbances consisting of visual hallucinations and other psychotic symptoms (*1*). This phenomenon has been widely investigated because the psychotic symptoms evoked by LSD-25 are similar to those of schizophrenic patients. Mescaline is another alkaloid long known to produce hallucinations and other psychological and somatic changes like those caused by LSD-25 (*2*). LSD-25 induces, in both experimental animals (*3*) and human beings (*4*), alterations of the electric activity of the brain, consisting of the disappearance or diminution of the slower waves, an increase in the average frequency and of fast low-voltage activity as well as a general diminution of voltage resulting in a flattening of the record.

We studied the effect of mescaline on the electric activity of the rabbit brain and found that it introduces changes that are practically identical with those resulting from LSD-25. It is interesting to note that there is a similarity in the alterations of the electroencephalogram (EEG) induced by these hallucinogenic substances and the records often obtained from schizophrenic patients (*5*). In fact, the choppy rhythm that Davis found in schizophrenic patients consists of low-voltage fast activity accompanied by a poor organization of the alpha rhythm.

The brain electric activity of the curarized, unanesthetized rabbit (the preparation used in the present studies) consists of two fundamental patterns: one, which is seen when the rabbit is undisturbed and resting quietly, consists of slow high-voltage waves and 14-cy/sec spindles; the other, observed when the animal is alerted by a sensory stimulation, reveals fast low-voltage cortical activity with a 4- to 6-cy/sec thalamic rhythm (*6*). This occurs when a neuronal system (mesodiencephalic activating system), which regulates diffusely the electric activity of the brain (*6*), is set into operation.

LSD-25 (10 to 15 μg/kg) and mescaline (10 to 20 mg/kg) induce a change of the electric activity of the brain, consisting in the first place in the elimination of the slow waves and the spindles typical of the resting pattern and, in the second place, in the persistent presence of fast low-voltage activity and the 4- to 6-cy/sec thalamic rhythm, practically identical with the picture that is seen in the alert status (Fig. 1).

Recently Fabing (*7*) reported that the psychotic symptomatology produced in human subjects with hallucinogenic amounts of LSD-25 disappeared after the administration of alpha-4-piperidyl benzhydrol hydrochloride (Frenquel) (*8*). The latter is a new nonhypnotic drug that renders animals less active and in human subjects produces promising results in the management of abnormal mental conditions (*9*).

In our experiments on the rabbit we administered alpha-4-piperidyl benzhydrol hydrochloride intravenously in doses between 8 and 24 mg/kg to animals that had received amounts of LSD-25 or of mescaline sufficient to cause the aforedescribed permanently alert change of

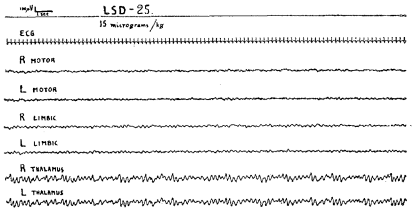

Fig. 1. Effect of LSD-25 on the cerebral electric activity of the rabbit. Notice the low-voltage fast activity in the motor cortex and the thalamic 4- to 6-cy/sec rhythm. Note also the absence of high-voltage slow waves and of spindles. Six monopolar leads from different cerebral structures, as indicated in the figure. Top tracing: electrocardiogram.

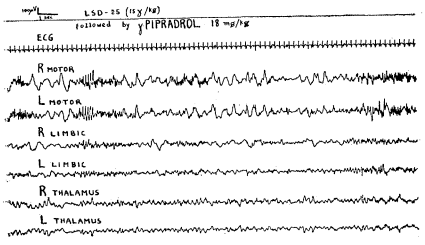

Fig. 2. The abnormalities induced by LSD-25 in the cerebral electric activity of the rabbit are corrected by administration of alpha-4-piperidyl benzhydrol hydrochloride (indicated in the figure as gamma-pipradrol). Notice the reappearance of the high-voltage slow activity and the 14-cy/sec spindles, predominantly in the motor cortex.

the electric brain activity. In all our experiments (five animals with LSD-25, five animals with mescaline) we observed that, within 2 to 10 min after the administration of alpha-4-piperidyl benzhydrol hydrochloride, the normal pattern of brain electric activity was restored. The slow waves and 14-cy/sec spindles, which were eliminated by the hallucinogenic drugs, returned after alpha-4-piperidyl benzhydrol hydrochloride (Fig. 2). The doses of the drug necessary to correct the abnormal electric activity ranged between 12 and 24 mg/kg. We found that there is a direct relationship between the amount of hallucinogen administered and that of alpha-4-piperidyl benzhydrol hydrochloride necessary to reverse the electric changes. Alpha-4-piperidyl benzhydrol hydrochloride when administered alone does not influence the EEG. Neither does it enforce the sleep pattern nor depress the mesodiencephalic activating system, the hyperactivity of which is responsible for the pattern of alertness (*10*).

Di-isopropylfluorophosphate (DFP), amphetamine and Meratran (alpha-2-piperidyl benzhydrol hydrochloride) are other drugs that, like the hallucinogenic substances, evoke a permanent pattern of alertness (*11*). We administered alpha-4-piperidyl benzhydrol hydrochloride to animals that had received enough DFP, amphetamine, and Meratran to produce a continuous alert electric pattern. In no instance, however, did alpha-4-piperidyl benzhydrol hydrochloride correct the effects of DFP, amphetamine, or Meratran, even though the last is a positional isomer of alpha-4-piperidyl benzhydrol hydrochloride. So far it seems that the described action of alpha-4-piperidyl benzhydrol hydrochloride in restoring normal electric patterns in the rabbit is limited to, and perhaps is specific for, the changes induced by the hallucinogenic drugs, LSD-25 and mescaline. Probably the antagonism between alpha-4-piperidyl benzhydrol hydrochloride and the hallucinogenic agents is restricted to the central nervous system, for we have observed that alpha-4-piperidyl benzhydrol hydrochloride does not correct the mydriasis associated with the action of LSD-25 or mescaline. Fabing (*7*) also observed the rectification of the psychic symptoms but not of the autonomic and other physiological alterations wrought by LSD-25.

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21 January 1955

Influence of Calcium on Mobility of the Electrophoretic Components of Chicken Blood Serums

The increase in the amount of nondiffusible calcium present in the blood serums of the laying hen has been confirmed many times (*1*). The same relationship has been shown to hold for young hens and cockerels under the influence of the female sex hormones. It has been demonstrated that the serum proteins of the laying hens or hormone-treated birds contain electrophoretic components not present in the serums of the nonlaying birds (*2–4*). Evidence indicating that the variations in the nondiffusible calcium of chicken serums can be associated with the change in concentration of these electrophoretic components has been reported (*5*). A method for measuring P^{32} distribution in the electrophoretic components of protein mixtures has been reported (*6*), and by means of this method it has been shown that the leading component of laying-hen serums and of hormone-injected cockerel serums was extremely rich in phosphorus (*7*).

The high phosphorus content of this leading fraction makes possible the determination of the position of this component under different conditions, even though it may be masked by the fact that it is migrating at the same rate as other components of the serum. By employing the afore-mentioned electrophoretic-radiochemical technique, the effect of increasing concentrations of calcium upon the mobility of this component has been determined (*8*).

The blood serum was prepared from the blood of 8-wk old cockerels injected with 2.0 mg of diethylstilbestrol per day for 5 days. Each chick was fed 0.5 mc of P^{32} daily for 5 days. The electrophoretic (*2*) and radiochemical (*6, 7*) techniques have been described elsewhere. The electrophoreses and previous dialyses were carried out with a borate buffer that contained graded amounts of calcium. The concentrations of calcium employed are indicated in Fig. 1.

When the leading protein fraction was not apparent in the electrophoretic picture but the P^{32} activity associated with it was found to be present in some other fraction, it was assumed that the two fractions were migrating at the same rate. In addition, the areas associated with the electrophoretic components were also determined; when the component containing the extra P^{32} activity had increased in area, the afore-mentioned assumption was considered valid. By this method the mobility associated with this high-phosphorus leading protein component and the other protein components was determined in buffer solutions containing various levels of calcium.

Results of this experiment (Fig. 1) show that the mobility of fraction I, the fastest moving component in buffer containing no calicum, was drastically changed by the addition of calicum to the buffer. The mobilities of the other five

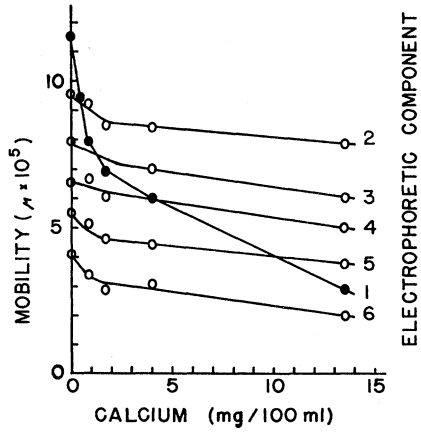

Fig. 1. Mobilities of the electrophoretic components in the serums of diethylstilbestrol-treated cockerels in a borate buffer, *p*H 8.6, containing graded amounts of calcium.