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INCOMPATIBILITIES OF SOME IMPORTANT NEWER CHEMICALS.*

BY CHARLES F. LANWERMEYER.

In his daily compounding of prescriptions, the pharmacist is often confronted with the problem of incompatibility. The physician knows what action he needs in the particular case and prescribes the individual drugs in combination; but it is up to the pharmacist to make an elegant, chemically and physically compatible mixture. The various textbooks on pharmacy devote some space to incompatibilities and there are also books like Ruddiman's "Incompatibilities" devoted exclusively to this subject.

In this day of multifarious new chemical production, the authors of these texts would have to publish annual editions in order to keep step with the manufacturers. It was in order to fill this gap that the following work was undertaken.

This work presents the Literature References in a condensed form as well as the results obtained by the author in making mixtures such as the dispensing or manufacturing pharmacist might be asked to compound. The following chemicals, which are listed either in the U. S. P. or in the "New and Nonofficial Remedies," were used in this study: Acriflavine (Base), Acriflavine Hydrochloride, Amidopyrine, Barbital, Sodium Barbital, Benzocaine, Butesin, Butyn, Ephedrine Hydrochloride, Ephedrine Sulphate, Neonal, Phenobarbital and Procaine Hydrochloride. References to these items in the literature were examined, and combinations with other drugs were made up and allowed to age in the laboratory.

AMIDOPYRINE.

(Also known as Pyramidon and Amidozone.)

The solubility of Amidopyrine stated in the U. S. P. is 1 Gm. in 18 cc. of water. Other texts claim 1 in 11 (E) (X), 1 in 20 (Y), 1 in 9 (B). The author found that the U. S. P. solubility is correct. According to *Comptes rend.*, 1927-185, p. 284, "the difference in water solubilities was accounted for because of this often being a mixture of A and B Pyramidon."

It is incompatible with acacia producing a colored solution (R). This is due to the oxydase present, and can be prevented by heating the acacia to 85° C. which destroys the oxydase (S). A blue-violet color is produced by many oxidizing agents like ferric chloride, silver nitrate, nitric acid, spirit of nitrous ether, lead dioxide,

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* Scientific Section, A. PH. A., Miami meeting, 1931.

iodine solutions and some enzymes (P). Mixed with aspirin even in two separate granulations (as in tablet manufacture) it will become yellow in a few months. If mixed and moistened in granulation it will become sticky and stick on the compressing machine (P). It is incompatible with amyl nitrite and apomorphine (BB). Mixed with citric or tartaric acids it forms a sticky mass in a short time, but with salicylic acid this occurs at once. With salol it becomes yellow colored in a short time. Dissolved in Elixir Lactated Pepsin it changes the color of the elixir to purple and precipitates on standing. Dissolved in Essence of Pepsin it remains unchanged when fresh but precipitates on standing. With mercury bichloride it masses and becomes grey colored. With neonal it becomes sticky and develops a slight odor. Its aqueous solution has a slightly alkaline reaction. Mixed with the following there is no apparent change: Antipyrine, acetphenetidin, ammonium chloride, borax, cinchophen, tannic acid, potassium acetate, sodium phosphate, sodium biphosphate, lead acetate, methenamine, menthol, phenolphthalein, potassium bromide, potassium iodide, sodium salicylate, extract of cascara and calomel.

Acriflavine (Base).

Acriflavine is soluble in three parts of water (R), incompletely soluble in alcohol (T), nearly insoluble in ether, chloroform, liquid petrolatum and fixed and volatile oils (R). Its solutions have a neutral reaction (P), hydrochloric acid destroys its fluorescence (P). Solutions precipitate with silver nitrate (P), sodium hydroxide gives an orange precipitate in dilute solutions (P). Solutions 1 to 1000 can be made in Normal Saline Solution (X). A solution in oil can be made by dissolving 2% (based on the final) in a small amount of alcohol and then diluting with castor oil q. s. (X).

Acriflavine Hydrochloride.

(Also known as Trypaflavine.)

Acriflavine Hydrochloride is soluble in three parts of water (BB), although commercial samples vary considerably (T). It is soluble in alcohol 1 in 40 (BB), insoluble in ether, chloroform, liquid petrolatum, fixed or volatile oils (T), insoluble in oleic acid and eucalyptol (BB). Its solutions have a distinct acid reaction making it incompatible with carbonates or bicarbonates (T). It is incompatible with Dakin's Solution and other chlorine antiseptics, mercury bichloride and phenol in solution (BB). A solution in Normal Saline Solution is clear when freshly prepared, but precipitates in 24 hours although if the saline solution contain 5% salts, precipitation takes place at once (BB). It is compatible with an 0.5% sodium citrate solution. Its solution in water is stable even when boiled or autoclaved at 130° C. Stains can be removed with a little dilute hydrochloric or sulphurous acid followed by washings with water.

Anesthesin.

(Also known as Benzocaine, Ethylaminobenzoate or Keloform.)

Heated with soluble alkali hydroxides and carbonates Anesthesin decomposes into alcohol and *p*-aminobenzoic acid (P). Aqueous solutions precipitate with iodine (P), small amounts of hydrochloric acid increase its solubility (P). It is

incompatible with acids or acid salts in solution (W). Its aqueous solution is decomposed by boiling but solutions in oil can be boiled (W). If used in combinations containing perfume materials like vanillin or heliotropin even in small amounts, discoloration will result. Mixed with bismuth subnitrate it discolors in a few months; with resorcin it forms a sticky mass and discolors on standing. Mixed with the following substances no apparent change takes place: Bismuth subgallate, zinc sulphocarbolate, sodium bicarbonate, magnesium oxide, bismuth subsalicylate, salol, sodium thiosulphate, acetanilid, boric acid, tincture ferric chloride, milk of bismuth, milk of magnesia, calomel, cerium oxalate and ammonium bromide.

Barbital.

(Also known as Veronal, Barbitone, Hypnogen or Malonal.)

Barbital and acetphenetidin are antagonistic physiologically, as tested on guinea pigs (*Arch. Expt. Pharm. & Pharmacol.*, 116-140-6 (1926). Antipyrine is antagonistic to the sedative effect of barbital, but the stimulating effect of the two is synergistic (*Arch. Expt. Pharm. & Pharmacol.*, 114-313-26 (1926). Heating with alkali carbonates or hydroxides decomposes it, liberating ammonia (P). It darkens with calomel slowly; but when moist or if sodium bicarbonate is present it darkens immediately (P). With alkalies it forms salts that are soluble in water (P).

Barbital Sodium.

(Also known as Medinal.)

Barbital Sodium is incompatible with ammonium salts (*viz.*, ammonium bromide) giving off ammonia and precipitating barbital; (barbital itself is not changed in this way (H). It is incompatible with acid salts, morphine hydrochloride and with solutions containing fruit essences on account of the acid present (H). With Tincture of Cinchona it precipitates out the alkaloids but the reaction takes 24 hours.

Butesin.

(Also known as Scuroforme.)

Butesin is almost insoluble in water and when boiled in it is slowly hydrolyzed; it is soluble in dilute acids, alcohol, chloroform, ether, benzene and fatty oils. Its solution in oil is not decomposed by heat. It is incompatible with silver nitrate (R). It dissolves very readily in oils of cassia, cloves and wintergreen; with resorcin it masses at once and changes to a green sticky mass. It is insoluble in liquid petrolatum. With the following in dry mixtures there is no apparent change:—Bismuth subnitrate, calomel, betanaphthol and sulphur; also sulphur ointment.

Butyn.

Butyn is incompatible with alkali carbonates and hydroxides precipitating out the free base, with soluble bicarbonates precipitating out the carbonate (R); it precipitates with the general alkaloidal reagents (P); it is incompatible with iodine solution, barium chloride and picric acid (R). It decolorizes potassium permanganate solution. It is incompatible with chlorides or saline solutions, but isotonic solutions can be made using potassium sulphate in the following amounts:

½% solution requires 1.34 Gm. K_2SO_4 per 100 cc.
1% solution requires 1.21 Gm. K_2SO_4 per 100 cc.
2% solution requires 0.97 Gm. K_2SO_4 per 100 cc.
5% solution requires 0.24 Gm. K_2SO_4 per 100 cc.

It is incompatible with silver protein preparations in solution, precipitating yellowish brown at once. With lead acetate solution it precipitates lead sulphate at once but makes a good shake mixture. With Fluid Extract of Hydrastis, Fluid Golden Seal Compound and Solution Hydrastine there is no apparent change.

Ephedrine Hydrochloride.

Ephedrine hydrochloride is soluble in water 1 to 7, in alcohol 1 to 8, the solutions being neutral. It is insoluble in ether (BB) (T). It is incompatible with silver salts, causing precipitation; with amidopyrine in solution it precipitates; and it is incompatible with Syrup of Wild Cherry. With the following there is apparently no change: Elixir Euphorbia Compound, potassium bromide, potassium iodide, aspirin, amidopyrine (dry), acetanilid, acetphenetidin, barbital, phenobarbital, neonal, calomel, sodium bicarbonate, magnesium carbonate and oxide, phenolphthalein, quinine sulphate, sodium salicylate, neocinchophen, methenemine, potassium acetate, caffein, caffein citrated, Elixir Terpin Hydrate, Brown's Mixture and Syrup of White Pine Compound.

Ephedrine Sulphate.

Ephedrine sulphate has practically the same properties as the hydrochloride, except that it is less soluble in cold alcohol, is compatible with silver salts and is incompatible with potassium iodide causing yellow discoloration of the solution, forming a precipitate; with Neonal it causes a strong ethereal odor, with methenemine a strong urine-like odor; with potassium acetate a strong odor is also developed. With all the other combinations mentioned above under Ephedrine Hydrochloride there was no apparent change.

Neonal.

Neonal is incompatible with acetanilid developing a foreign odor. A mixture with amidopyrine becomes sticky and develops an odor. With calomel, especially if any moisture is present, the mixture turns grey although if perfectly dry there is apparently no change. With salicylic acid it develops an odor. With the following there is apparently no change: Acetphenetidin, ammonium bromide, bismuth subnitrate, magnesium oxide, sodium bicarbonate, sodium bromide and sodium salicylate.

Phenobarbital Sodium.

Phenobarbital sodium is unstable unless stored in air-tight containers in the dark (H). In aqueous solution, on standing or by boiling, it is partly decomposed with formation of phenyl ethyl acetyl urea, which precipitates out (Y). On account of its alkaline reaction it has the same incompatibilities as the alkalies, and may therefore precipitate alkaloids out of solutions of their salts such as caffeine and strychnine out of elixirs and syrups (L). It is incompatible with ammonium bromide in solution, precipitating out the phenobarbital (H), the supernatant liquid having an ammonia odor (L)

PROCAINE HYDROCHLORIDE.

(Also known as Ethocaine, Kerocaine, Neocaine, Novocaine and Syncain.)

Novocaine is incompatible with iodine and with picric acid solution (D). Also with mercuric chloride, gold chloride and Mayer's reagent (P), and with silver salts (R). With sodium carbonate or hydroxide solutions, the base separates out as an oily liquid (D) (P). With sodium bicarbonate there is no change (P). It is incompatible with tannin, calomel, potassium dichromate and permanganate (BB). Its solutions can be sterilized at 100° C. without change but are damaged at 120° C.

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PHARMACEUTICAL RESEARCH DEPARTMENT,
ABBOTT LABORATORIES,
NORTH CHICAGO, ILL.

Among other things, a successful Pharmacy Week display is dependent on a definite purpose. After selecting a topic, the next important thing is to "stick to your text."