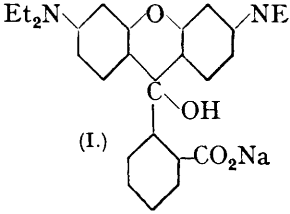
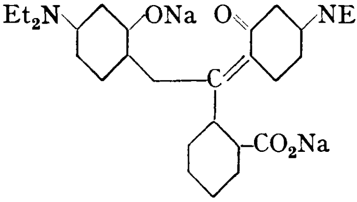
297. *The Blue Sodium Salt of Rhodamine-B and some Related Substances.*

By William R. Brown and Frederick A. Mason.

By the action of sodium hydroxide upon rhodamine-B, Wacker (*Z. Farb. Ind.*, 1907, 201) obtained a dark blue crystalline sodium salt to which he assigned the formula (I). Von Baeyer pointed out that this offered no explanation of the colour of the salt, and from his previous work upon the action of alkali upon fluorescein and dinitrofluorescein (*Annalen*, 1876, **183**, 1, 32; 1910, **372**, 111; see also Hewitt and Perkins, J., 1900, **77**, 1324; Hewitt and Woodford, J., 1902, **81**, 895), he suggested that, in this case also, the pyrone ring had been ruptured with the formation of a disodium salt of the structure (II). (In the formula given by von Baeyer the tetramethylrhodamine is indicated; we have been unable to confirm this, as this compound did not yield a blue salt under the foregoing conditions.)

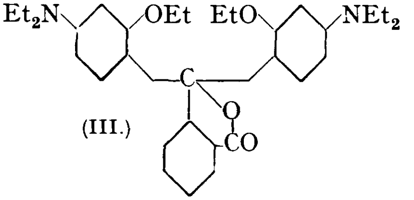

(I.)

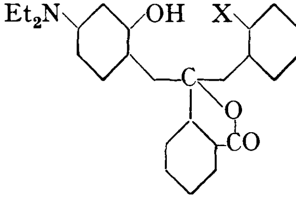

(II.)

The " blue salt " was not analysed by von Baeyer or by Wacker, nor were its general properties further investigated; hence, it seemed of interest to examine the behaviour of rhodamine-B and related substances towards alkalis and the chemical properties of the blue salt, and also to attempt to synthesise phthaleins of constitutions analogous to (II) and (III), the latter being the formula put forward originally by Monnet for anisoline (G.P. 66238; *Bull. Soc. chim.*, 1892, **7**, 523), obtained by the action of ethyl chloride and alkali upon rhodamine-B (see also Bernthsen, *Chem. Ztg.*, 1892, **16**, 1956). The blue salt could only be obtained by Wacker's original method, although several modifications were tried in order to obtain it free from inorganic salts, as it is practically insoluble in most non-aqueous solvents, except pyridine, and in alcohol or water it immediately re-forms rhodamine-B. Estimation of the sodium content indicated, however, that it was in fact a disodium salt, in agreement with von Baeyer's formula. When kept in a loosely stoppered bottle, it gradually absorbed moisture, becoming red and acquiring a characteristic *iso*nitrile odour.

Attempts to prepare blue alkali salts of other rhodamines gave negative results, so that rhodamine-B appears to be unique in this respect. In view of the very pronounced tendency to re-form the oxo-ring found in the case of rhodamine-B, it is somewhat remarkable that the rosamine containing unalkylated amino-groups (derived from benzaldehyde and *m*-aminophenol) is formed from the corresponding triphenylmethane compound only on heating with concentrated sulphuric acid, the free dihydroxy-compound showing no tendency to lose water spontaneously (Bayer & Co., G.P. 62574), and in the same way the corresponding *p*-dimethylaminorosamine can be obtained from 2′ : 2″-dihydroxy-4′ : 4″ : 4‴-hexamethyltriaminotriphenylmethane only on heating with concentrated sulphuric acid (Noelting and Gerlinger, *Ber.*, 1906, **39**, 2053). A substance of formula (II) might be expected to yield phenolic ethers or esters with suitable alkylating or acylating agents, but all attempts to prepare such derivatives directly from the blue salt resulted in the immediate regeneration of rhodamine-B itself.

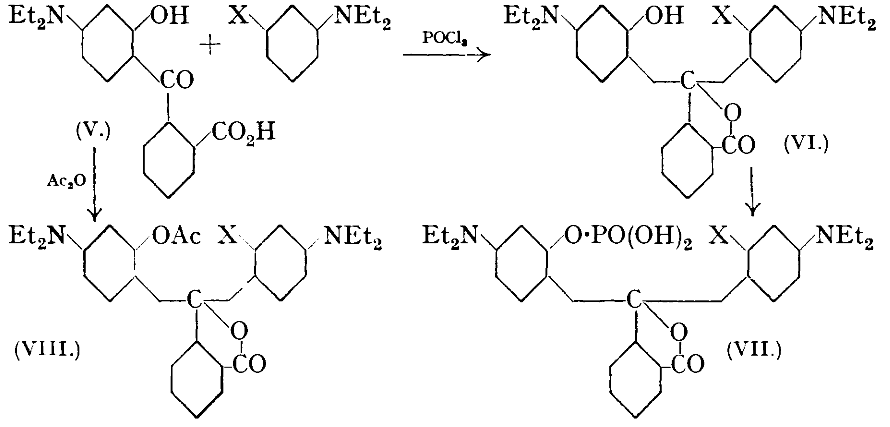
In pursuance of our second objective, several substances were prepared of the general structure (IV) (X = H, OH, OMe, O·CO_2Et, etc.). The most obvious method of preparation (if von Baeyer's formula be correct), *viz.*, that of treating the blue sodium salt of rhodamine-B with an alkylating or acylating agent in a neutral or basic solvent, gave completely negative results, the reagents simply acting as condensing agents, with immediate re-formation of rhodamine-B. The only practicable method, therefore, was to attempt


(III.)


(IV.)

the condensation of 4′-diethylamino-2′-hydroxy-*o*-benzoylbenzoic acid (V) with various amines, which in the case of *m*-diethylaminophenol affords rhodamine-B itself.

A. *Condensations by means of phosphoryl chloride.* The acid was condensed with the following substances : dimethyl- and diethyl-aniline, ethylbenzylanilinesulphonic acid, *m*-methoxy- and *m*-ethoxy-diethylaniline, according to the method of G.P. 85931, *i.e.*, heating the components together in benzene or toluene solution in presence of phosphoryl chloride. Condensation occurred readily in all cases, with the production of substances which were soluble in alkali to blue-violet solutions and appeared to be the desired analogues of the " blue salt," *e.g.*, (VI).



On examination, however, they were all found to consist of pairs of substances, distinguished as the " A " series and the " B " series. Both types gave colourless solutions in acids, the " A " type affording green and the " B " type violet solutions in caustic alkalis, and in the cases of the methoxy- and ethoxy-derivatives, on reacidification rhodamine-B was formed (identified by its absorption spectrum).

The products were associated with much inorganic matter, particularly phosphorus, and all attempts at further purification failed. That the inorganic matter is chemically combined is shown by the ready solubility of the product in non-aqueous solvents such as benzene and chloroform. It appears possible that the " A " series may consist of phosphoric esters of the type (VII), the inorganic radical being eliminated by caustic alkali, but this point remains uncertain, as the substances could not be obtained pure and their further investigation appeared unprofitable.

B. *Condensations by means of acetic anhydride.* By the use of acetic anhydride, colourless, well-crystallised condensation products were obtained consisting of the acetyl derivatives of the desired compounds ; thus, from diethylaniline was formed the acetyl derivative of (VI ; X = H), *i.e.*, 4′ : *4″-bisdiethylamino-2′-acetoxydiphenylphthalide.*

A number of such derivatives were prepared and analysed. They fall naturally into two groups : (i) where the second component is an unsubstituted tertiary amine, *i.e.*, in addition to the foregoing compound, *4″-dimethylamino-4′-diethylamino-2′-acetoxydiphenylphthalide*, 4′-diethylamino-4″-ethylsulphobenzylamino-2′-acetoxydiphenylphthalide, and *4′-diethylamino-2′-acetoxyphenyl-4″-dimethylamino-α-naphthylphthalide* ; (ii) where the second component is an oxy-derivative, *e.g.*, *m*-methoxy- or m-*ethoxy*-diethylaniline or the corresponding ethyl carbonate, *i.e.*, 4′ : *4″-bisdiethylamino-2′-acetoxy-2″-ethoxy-* and 4′ : *4″-bisdiethylamino-2′-acetoxy-2″-methoxy-diphenylphthalides.*

Both types, (i) and (ii), were stable towards cold aqueous 10% sodium hydroxide, but on short treatment with alcoholic potassium hydroxide, even in the cold, the 2′-acetyl group was quickly hydrolysed, yielding the corresponding 2′-hydroxy-compound. In group (i) the hydrolysis products obtained were stable and acted as indicators of the *ortho*phthalein type, (VI ; X = H), for instance, changing from colourless in acid to deep violet in alkali at p_H 9—10. In other cases, the colour change occurred over a range from

p_H 9 to 11. In the compounds of group (ii), warm alcoholic caustic alkali removed not only the acetyl group but also the alkyl group, with formation of the rhodamine, thus confirming the very strong tendency towards the formation of the stable pyrone structure noted throughout. With cold dilute methyl-alcoholic barium hydroxide solution, a purple liquid was formed, changing slowly on standing, and rapidly on warming, to the typical rhodamine red solution.

Whilst the results of the present investigation cannot be regarded as definitive, the evidence obtained, in particular the behaviour of the phthaleins of type (ii) with alcoholic barium hydroxide, suggests that von Baeyer's formula for the blue salt of rhodamine-B is correct.

EXPERIMENTAL.

The Blue Sodium Salt of Rhodamine-B.—Recrystallised rhodamine-B (10 g.) in 20 c.c. of boiling water, slightly acidified with hydrochloric acid, was filtered into 40% sodium hydroxide solution (175 c.c.) with shaking. When heated to 90°, the violet precipitate became deep blue and crystalline, and was then collected on a Buchner funnel. After being washed with 40% sodium hydroxide solution, the product was sucked dry in a current of well-dried air, and then placed in a vacuum desiccator over potassium hydroxide. Attempts to obtain the product free from sodium chloride by the use of the rhodamine base did not give a satisfactory product. The use of alcoholic sodium ethoxide, as recommended by Hewitt and Perkins (*loc. cit.*), also failed to yield the blue salt. The product so obtained was not analytically pure but the percentage of sodium agreed approximately with that calculated for the disodium salt. A dilute solution of the substance in pyridine (1 : 20,000) showed a strong characteristic absorption band with a peak at $\lambda = 600$ μμ. A very dilute solution in benzene was unstable, but showed a maximum absorption at $\lambda = 635$ μμ. All attempts at alkylating or acylating the blue salt by means of ethyl bromide, methyl sulphate, toluene-*p*-sulphonic ester, or benzoyl chloride caused immediate formation of rhodamine-B.

*4′-Diethylamino-2′-hydroxy-*o*-benzoylbenzoic Acid.*—The process of G.P. 85931 was examined to determine the most suitable solvent and the optimum time of heating, benzene, toluene, and xylene being used for periods varying from 2 to 8 hours. Toluene gave the best results : phthalic anhydride (30 g.; 0·2 mol.) and *m*-diethylaminophenol (33 g.; 0·2 mol.) were heated together for 5 hours in boiling toluene (150 c.c.). The crude red acid which separated was removed at once from the hot liquid, washed successively with small volumes of hot toluene and about 70 c.c. of methylated spirit to remove tar, and recrystallised from methylated spirits; pinkish crystals, m. p. 170—180° (decomp.); crude yield, 70—80%.

Methyl ester. The acid (20 g.) was suspended in dry methyl alcohol (100 c.c.), the mixture cooled in a freezing mixture, mechanically stirred, and hydrogen chloride passed in. The thick paste formed was gradually converted into a pale yellow solution, and after standing for some hours was heated to 30° for 10 minutes, and then poured into iced dilute ammonia to remove unchanged acid; the insoluble cake of ester formed colourless platelets from methyl alcohol, m. p. 124° (Found : C, 69·3; H, 6·7; N, 4·4. $C_{19}H_{21}O_4N$ requires C, 69·7; H, 6·4; N, 4·3%).

Attempts to prepare the methyl ether of the same acid, either by direct alkylation or by condensing together the methyl ether of *m*-diethylaminophenol and phthalic anhydride by means of aluminium chloride, were unsuccessful.

A. *Condensations of 4′-Diethylamino-2′-hydroxy-*o*-benzoylbenzoic Acid with Tertiary Amines by Means of Phosphoryl Chloride.*—The following example, with dimethylaniline, is typical of all the condensations. 5 G. of the acid and 2 g. of dimethylaniline were added to toluene (20 c.c.), and phosphoryl chloride (5 g.) added. After the initial reaction had taken place with a slight rise in temperature, the mixture was heated to 120° in an oil-bath for 15 minutes, the excess of toluene decanted off, and the remainder removed by steam-distillation. From the filtered aqueous solution, the condensation product was precipitated by the addition of sodium acetate (50 g.) in water (100 c.c.). The product was purified by solution in dilute hydrochloric acid (charcoal) and reprecipitation by sodium acetate, the final product being filtered off and dried; yield 5 g. This was boiled with methyl alcohol (150 c.c.) and cooled, the sparingly soluble product, A_3, being then filtered off; it formed, when dry, a pale green amorphous powder affording green solutions in alkalis.

The soluble product B_3, was recovered by pouring the alcoholic mother-liquor into a solution of sodium acetate (100 g.) in water (200 c.c.), and formed an amorphous powder giving a violet solution in alkalis. Both A_3 and B_3 formed non-crystalline hydrochlorides and contained phosphorus; they were not pure enough for analysis.

B. *Condensations of 4′-Diethylamino-2′-hydroxy-*o*-benzoylbenzoic Acid by Means of Acetic Anhydride.*—(a) *With diethylaniline.* The acid (9 g.) and diethylaniline (4·5 g.) were dissolved in acetic anhydride (45 c.c.) and the whole refluxed for 3 hours. The cooled product was stirred with ice-water until the hydrolysis of the acetic anhydride was complete; the colourless 4′ : 4″-*bisdiethylamino-2′-acetoxydiphenylphthalide* (12 g.) was recrystallised from methyl alcohol; yield 10 g. (77%); m. p. 136—137° (Found : C, 73·5; H, 7·2; N, 5·8. $C_{30}H_{34}O_4N_2$ requires C, 74·1; H, 7·0; N, 5·8%).

Hydrolysis. 2 G. of the condensation product were warmed for a short time with methyl alcohol (20 c.c.) and 20% methyl-alcoholic potassium hydroxide (5 c.c.). The mixture was poured into dilute acetic acid and the pale blue precipitate filtered off; after purification by redissolution in dilute hydrochloric acid, precipitation with sodium acetate, and drying, the resultant 4′ : 4″-bisdiethylamino-2′-hydroxydiphenylphthalide formed a pale blue amorphous powder, soluble to a colourless solution in acids and a deep violet solution in alkalis of $p_H > 9$.

The absorption spectrum showed a maximum at 580—590 μμ. The substance still contained traces of inorganic matter and was not analysed.

(b) *With dimethylaniline.* The preparation was carried out as in the previous case, the resultant *4″-dimethylamino-4′-diethylamino-2′-acetoxydiphenylphthalide* separating from methyl alcohol at first as an oil, which solidified to colourless crystals, m. p. 130—131° from methyl alcohol (Found : C, 73·2; H, 6·9; N, 6·2. $C_{28}H_{30}O_4N_2$ requires C, 73·3; H, 6·6; N, 6·1%).

On hydrolysis with alcoholic potassium hydroxide it yielded the hydroxy-compound, giving a change, colourless → purple, at p_H 9—10.

(c) *With ethylbenzylanilinesulphonic acid.* The product obtained could not be crystallised and was not analysed. On hydrolysis with alcoholic potassium hydroxide, it yielded an indicator changing from colourless to violet at p_H 10—11.

(d) *With dimethyl-α-naphthylamine.* With 1·7 g. of dimethyl-α-naphthylamine and 3 g. of the acid, 2 hours' boiling sufficed to effect the condensation, which was accompanied by much rhodamine formation. 3·2 G. of *4′-diethylamino-2′-acetoxyphenyl-4″-dimethylamino-α-naphthylphthalide*, m. p. 122—123° (Found : C, 75·8; H, 6·7; N, 5·2. $C_{32}H_{32}O_4N_2$ requires C, 75·6; H, 6·3; N, 5·5%), were obtained. On hydrolysis it yielded 4′-diethylamino-4″-dimethylamino-2′-hydroxyphenylnaphthylphthalide (?) which gave a change from colourless to orange-brown at p_H 9—10, showing a maximum absorption at $\lambda = 470$ μμ.

Attempts to condense 4′-diethylamino-2′-hydroxy-*o*-benzoylbenzoic acid with *N*-ethylcarbazole, *m*-nitrodimethylaniline, acetanilide, monoethyl- and diethyl-*o*-toluidine yielded no identifiable products capable of giving a coloration with caustic alkali, so condensation had apparently not been effected.

(e) *With* m*-ethoxydiethylaniline.* *m*-Diethylaminophenol (115·5 g.; 0·7 mol.), dissolved in 10% aqueous sodium hydroxide (350 c.c.; 0·875 mol.) diluted with water (700 c.c.), was treated with ethyl *p*-toluenesulphonate (175 g.; 0·875 mol.), and the mixture heated on the water-bath at 95° for ½ hour until the odour had disappeared. The m*-ethoxydiethylaniline*, after extraction by ether, was distilled under diminished pressure; it formed a colourless oil, b. p. 148°/15 mm.; yield 113 g. (87%) (Found : C, 74·1; H, 9·9; N, 7·5. $C_{12}H_{19}ON$ requires C, 74·6; H, 9·8; N, 7·3%).

4′-Diethylamino-2′-hydroxy-*o*-benzoylbenzoic acid (5 g.), *m*-ethoxydiethylaniline (3·2 g.), and acetic anhydride were boiled together for 4 hours, and the product worked up as before yielding 4·3 g. of product. The resultant 4′ : *4″-bisdiethylamino-2′-acetoxy-2″-ethoxydiphenylphthalide* was almost insoluble in methyl alcohol, but formed colourless crystals from ethyl alcohol or light petroleum, m. p. 206—208° (Found : C, 72·2; H, 7·3; N, 5·4. $C_{32}H_{38}O_5N_2$ requires C, 72·5; H, 7·2; N, 5·3%). It was unattacked by aqueous alkali, but with alcoholic potassium hydroxide in the cold, or more rapidly on warming, both the acetyl and the ethyl group were eliminated, with formation of rhodamine-B.

(f) *With* m*-methoxydiethylaniline.* This was effected as with the ethyl ether, some rhodamine formation being also noted. The resultant colourless crystals of 4′ : *4″-bisdiethylamino-2′-acetoxy-2″-methoxydiphenylphthalide* had m. p. 176—177°, from methyl alcohol (Found : C, 71·4; H, 7·0; N, 5·5. $C_{31}H_{36}O_5N_2$ requires C, 72·1; H, 7·0; N, 5·8%). The alcoholic mother-liquor was pale blue, turning rhodamine-red on standing. Possibly this may have been due to a small amount of the unacetylated methyl ether. The behaviour with alkalis was the same as that of the ethyl ether. Rhodamine formation also took place rapidly on warming the substance for a short time with concentrated sulphuric acid.

The authors' thanks are due to the British Dyestuffs Corporation, Ltd., and to the Clayton Aniline Co., Ltd., for generous gifts of chemicals.

COLLEGE OF TECHNOLOGY, MANCHESTER.

[*Received, June 23rd,* 1933.]