NOTES.

Some Pyridine and Quinoline Derivatives. By VLADIMIR A. PETROW.

THE following miscellaneous experiments were carried out with the object of preparing naphthyridine derivatives. They were completed prior to the publication of Kermack and Weatherhead (*J.*, 1942, 726).

(a) *4-Anilinopyridine Derivatives.*—4-Chloropyridine (25 g.) and aniline (21 g.) were heated under reflux on a water-bath. Vigorous reaction occurred after *ca.* 15 minutes. After 1 house the crystalline product was dissolved in water, ammonia added in excess, the product collected, dried and extracted with hot benzene (700 ml.). The insoluble fraction gave *4-anilinopyridine hydrochloride* (6·5 g.), flat needles from alcohol–ligroin, m. p. 227—228° (Found: C, 64·6; H, 5·4; N, 14·3; Cl, 17·3. $C_{11}H_{11}N_2Cl$ requires C, 64·0; H, 5·3; N, 13·6; Cl, 17·3%). The benzene extract on concentration gave 4-anilinopyridine, m. p. 175—176° (22·5 g.) (Kermack and Weatherhead, *loc. cit.*, give m. p. 173°). A solution of the base in conc. sulphuric acid gave an intense violet colouration with a trace of potassium nitrate and an immediate reddish-purple colouration with potassium dichromate. Neither the *acetyl* derivative, flat plates from alcohol–ligroin, m. p. 112—113° (Found: C, 73·6; H, 5·6; N, 13·1. $C_{13}H_{12}ON_2$ requires C, 73·7; H, 5·7; N, 13·2%), nor the *benzoyl* derivative, prismatic needles from benzene–ligroin, m. p. 166—167° (Found: C, 78·8; H, 5·1; N, 10·2. $C_{18}H_{14}ON_2$ requires C, 78·9; H, 5·0; N, 10·4%), underwent cyclisation when heated with anhydrous zinc chloride at 300° for 3 hours.

(b) *N-(4'-Pyridyl)-anthranilic Acid.*—Anthranilic acid (6·8 g.) in glacial acetic acid (20 ml.) was treated with 4-chloropyridine (5·7 g.) under reflux for 3 hours. When cold, the product was collected and crystallised from acetic acid containing a few drops of conc. hydrochloric acid. *N*-(4'-Pyridyl)-anthranilic acid hydrochloride formed stout needles, m. p. 282—283° (Found: Cl, 14·2. Calc. for $C_{12}H_{10}O_2N_2,HCl$: Cl, 14·2%) (Kermack and Weatherhead, *loc. cit.*, give m. p. 185°). The free *acid*, obtained by treating the hydrochloride (1·0 g.) in dilute alcohol with crystalline sodium acetate (600 mg.), formed needles from aq. alcohol, m. p. 283—284° (Found: C, 66·8; H, 4·7; N, 12·9. $C_{12}H_{10}O_2N_2$ requires C, 67·3; H, 4·7; N, 13·1%). Attempts to effect ring closure were unsuccessful.

(c) 4-Anilinolutidinecarboxylic acid (Michaelis, *Annalen*, 1909, **366**, 348) could not be cyclised.

(d) 2-Chloro-5-nitropyridine (3·2 g.) and anthranilic acid (2·8 g.) were heated in glacial acetic acid (25 ml.) for 3 hours and the cooled solution poured into dilute sodium acetate solution. The *product*, crystallised from alcohol, formed golden-yellow plates, m. p. 197·5—198·5° (Found: C, 59·9; H, 2·9; N, 17·2. $C_{12}H_7O_3N_3$ requires C, 59·8; H, 2·9; N, 17·4%). The compound was soluble in aqueous alkalis and was reprecipitated unchanged by acids; it was unchanged on being heated with phosphorus oxychloride. Although condensations of this type were originally thought to give rise to 1-aza-acridones (Reissert, *Ber.*, 1895, **28**, 119; cf. also Räth, *Annalen*, 1931, **486**, 284), there is little doubt that the products are actually derivatives of 2 : 3-dihydrobenz-4-quinazolone (Seide, *Annalen*, 1924, **440**, 314). The properties of the compound obtained from 2-chloro-5-nitropyridine (above) are consistent with its formulation as a nitrobenz-2 : 3-dihydro-4-quinazolone.

(e) *N*-(3′-Pyridyl)-anthranilic acid, m. p. 237—238°, was prepared by heating anthranilic acid (4 g.), 3-bromopyridine (6·4 g.), anhydrous potassium carbonate (4 g.), copper bronze (200 mg.) and nitrobenzene (24 ml.) for 3 hours under reflux (Found: C, 67·0; H, 4·6. Calc. for $C_{12}H_{10}O_2N_2$: C, 67·3; H, 4·6%) (Kermack and Weatherhead, *loc. cit.*, give m. p. 238°).

(f) N-(3′-*Quinolyl*)-*anthranilic acid* was prepared by heating anthranilic acid (4 g.), 3-bromoquinoline (8·2 g.), anhydrous potassium carbonate (4 g.), copper bronze (200 mg.) and nitrobenzene (30 ml.) for 45 minutes under reflux. The nitrobenzene was removed in steam and the aqueous liquors acidified with acetic acid; the dark green crystalline precipitate was crystallised from alcohol in needles, m. p. 251—252° (Found: C, 72·6; H, 4·6; N, 10·8. $C_{16}H_{12}O_2N_2$ requires C, 72·7; H, 4·6; N, 10·6%). Heating the acid with sulphuric acid at 100° did not lead to ring closure but to the formation of a bright yellow sulphonic acid.

(g) When 2-chloro-5-aminopyridine was submitted to the Doebner pyruvic acid synthesis, the *diketopyrrolidine* derivative was obtained as sparingly soluble needles from spirit, m. p. 245—246° (Found: C, 59·9; H, 3·4. $C_{20}H_{14}ON_4Cl_2$ requires C, 60·6; H, 3·6%). B.P. 259,973 claims the formation of the naphthyridine derivative under essentially similar conditions.

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Note on the Purification and Resolution of dl-*Adrenaline.* By S. Pickholz.

Because of their high solubility, the common salts of adrenaline are not readily isolated in good yields, although sparingly soluble salts might be considered useful for the purification of deteriorated adrenaline, recrystallisation of which is not possible, as there is no suitable solvent.

It has been found that *dl*-adrenaline hydrogen oxalate is a suitable salt for such a purpose. It is easily prepared, stable when exposed to air or to elevated temperatures, and practically insoluble in organic solvents. It is much less soluble in water at the ordinary temperatures than other known salts and crystallises from it. The base is easily liberated from its salt in the usual way. It has been found that the hydrogen oxalate of *l*-adrenaline has a much greater solubility than that of the corresponding salt of *dl*-adrenaline in ethanol.

Although oxalic acid is used in the extraction of neutral *l*-adrenaline from the suprarenal glands (Abderhalden and Bergel, *Ber.*, 1904, **37**, 2024), the preparation and properties of the actual salt have not been described, but it is interesting to note that the solubility of *l*-adrenaline in absolute alcohol containing oxalic acid has been suggested as a test for the purity of *l*-adrenaline (P. Lebeau and G. Courtois, "Traité de Pharmacie Clinique," Paris, 1938, vol. 2, 448). No reference has been made to the different behaviour of the *dl*-base.

A new method of completing the resolution of adrenaline may be based on the above observation provided that the starting material is adrenaline partly resolved in the usual way with tartaric acid (Flächer, *Z. physiol. Chem.*, 1908, **58**, 189). It is unlikely that there is any question of spontaneous resolution (cf., H. Gilman, "Organic Chemistry," New York, London, 1943, I, 254). There is a marked difference in the m. p. of the hydrogen oxalates, that of *dl*-adrenaline being 191—192°, and that of *l*-adrenaline 173—174° (both in sealed tubes). It appears, therefore, that *dl*-adrenaline is not an externally compensated mixture but a racemic compound and should be termed *rac*-adrenaline. Similar cases, considering the great number of recorded resolutions, are somewhat uncommon (Fischer, *Ber.*, 1892, **25**, 1253; 1894, **27**, 3225; Ladenburg, *Annalen*, 1888, **247**, 8). The case described more recenly by Duschinsky (*Chem. and Ind.*, 1934, **53**, 10) is referred to as one of spontaneous resolution. The above conclusion is in agreement with conditions laid down by Ladenburg (*Ber.*, 1894, **27**, 3065) and Walden (*Ber.*, 1896 **29**, 1692) in their theoretical discussions on the differentiation between racemic compounds and optically inactive mixtures.

dl-*Adrenaline-hydrogen oxalate.* Finely powdered cryst. oxalic acid (6·5 g.) was dissolved in boiling absolute ethanol (30 c.c.) and to the hot solution was added with vigorous shaking *dl*-adrenaline (9·1 g.). The base dissolved quickly, and very soon coarse crystals separated. After standing for some hours at room temperature, the *hydrogen oxalate* was collected, washed with absolute ethanol and ether and dried at 100° (12·2 g.), m. p. 191—192° (decomp.) (in sealed tube) (Found: $H_2C_2O_4$, 32·7. $C_9H_{14}O_3N,C_2H_2O_4$ requires $H_2C_2O_4$, 32·85%). The salt was practically insoluble in all common organic solvents but crystallised from hot 90% ethanol or from conc. solution in water.

l-*Adrenaline hydrogen oxalate.* Using the *l*-base instead of the *dl*-adrenaline and under the same conditions as above, no crystals separated in 72 hours. On seeding with either *l*- or *dl*-adrenaline hydrogen oxalate crystallisation began and was complete in about 24 hours (yield, 3 g. of *l*-salt), m. p. 173—174° (decomp.) (in sealed tube).

Solubilities in water. *l*- and *dl*-Adrenaline hydrogen oxalates (each 1 g.) were dissolved separately in water (5 c.c.) by warming. After filtering, the solutions were cooled. *dl*-Adrenaline hydrogen oxalate (0·85 g.) and the *l*-salt (0·2 g., only after seeding) separated.

Isolation of the adrenaline from the hydrogen oxalate. The salt was dissolved in water and the base precipitated by a slight excess of ammonia. For larger batches of the *dl*-oxalate the following method was employed. The oxalate (300 gm.) was dispersed in distilled water (*ca.* 2 litres) and conc. hydrochloric acid (50—100 c.c.) added. A clear solution was obtained from which adrenaline is precipitated by ammonia. When the formation of the oxalate followed by the purification of the adrenaline was carried out using a discoloured product, its colour and purity were improved.

Resolution by means of oxalic acid. The hydrogen oxalate of a partly resolved adrenaline was prepared in ethanol and left for about 18 hours in a refrigerator. The crystals were separated and the adrenaline liberated as above. The alcoholic mother liquors were concentrated under reduced pressure, diluted with water and ammonia added to liberate the base. The following results were obtained on six samples, the measurements being made by polarimetry:

Expt.	*l*-Adrenaline (%) in starting material (g.).	Adrenaline obtd. (g.) and *l*-adrenaline content (%). From crystals.	From mother-liquor.
1	80 (63%)	46 (57%)	30 (77%)
2	100 (76%)	62 (70%)	30 (94%)
3	228 (85%)	108 (75%)	110 (95%)
4	93 (90%)	20 (85%)	63 (96%)
5	97 (91%)	45 (85%)	49 (97·4%)
6	110 (95%)	21 (92%)	85 (98%)

The amount of separation depended not only on the degree of resolution of the starting material but also on the rapidity of crystallisation, the duration and degree of cooling and the amount of solvent used.

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The Synthesis of Cardiazole (Pentamethylenetetrazole) by the Action of Hydrazoic Acid on cyclo*Hexanone.* By N. B. CHAPMAN, H. MCCOMBIE and B. C. SAUNDERS.

$$C_5H_{10}{>}CO + 2N_3H \longrightarrow C_5H_{10}\langle \begin{matrix} C{=}N \\ N{-}N \end{matrix} \rangle N + H_2O + N_2$$

DESCRIPTIONS of the method of preparation are given in two patent specifications: E.P. 257,418 and E.P. 250,897. Both accounts are inexact and incomplete. The two accounts differ chiefly in the proportions of hydrazoic acid and *cyclo*hexanone used and in the range of catalysts mentioned. E.P. 257,418 specifies 2·5 mols. of hydrazoic acid to one of ketone, but we found that no tetrazole was produced under these conditions. E.P. 250,897 specifies 3·8 mols. of acid to one of ketone; we found that this gave good yields of tetrazole provided the other conditions were modified. E.P. 257,418 mentions only sulphuric acid as catalyst, but with this substance, we obtained only traces of tetrazole. Several of the many catalysts mentioned in E.P. 250,897 were tried, *e.g.*, anhydrous ferric chloride, gaseous hydrogen chloride, anhydrous zinc chloride, and of these ferric chloride was found to be the best. Scanty details were given of the method of isorating and purifying the product.

The preparation of solutions of hydrazoic acid in organic solvents is described in "Inorganic Syntheses," Vol. I, p. 78 (due originally to Frost, Cothran and Browne, *J. Amer. Chem. Soc.*, 1933, **55**, 3516), by von Braun (*Annalen*, 1931, **490**, 125) and by Rodebush *et al.* (*J. Amer. Chem. Soc.*, 1939, **61**, 2809). Von Braun claims theoretical yields of hydrazoic acid by the action of concentrated sulphuric acid on sodium azide in the presence of a small quantity of water. We have not obtained yields greater than 80% in spite of improvements on von Braun's technique. We, however, used a method of estimation specific for hydrazoic acid, whereas von Braun used simple acid–alkali titration, and would therefore estimate all acid impurities (*e.g.*, H_2SO_4) as hydrazoic acid. This may account for his high yields. We have found it necessary to estimate the hydrazoic acid in each preparation.

Some twenty experiments were carried out in order to investigate the following variable factors: the best method of obtaining solutions of hydrazoic acid in organic solvents; the rate of addition of ketone to the hydrazoic acid; the time, temperature, solvent and catalyst for the reaction; and the best method of isolating and purifying cardiazole.

As pure liquid hydrazoic acid is explosive all experiments were carried out behind a screen made of safety glass covered with wire gauze. We found, however, that the *solutions* were stable even when shaken vigorously. Because of the toxic nature of hydrazoic acid, a fume-chamber was used.

Preparation of Cardiazole.—Sodium azide (120 g.) was mixed with an equal weight of water in a 1-litre three-necked flask fitted with a thermometer, dropping-funnel and mechanical stirrer. A mixture (*ca.* 250 c.c.) of ligroin (60—80°) and benzene (15 : 85 by vol.) was then added. The mixture, immersed in ice, was stirred until the temperature fell to *ca.* 3° and then the calculated quantity of sulphuric acid (57 c.c., based on the equation $2NaN_3 + H_2SO_4 = Na_2SO_4 + 2N_3H$) was added from the dropping-funnel, at such a rate that the temperature did not rise above 10°. When all the acid had been added, stirring was stopped and the semi-solid mass in the flask broken up thoroughly. The flask was then tightly corked and vigorously shaken at intervals over about 2 hours. (This shaking is much more effective than the stirring mentioned by von Braun, in bringing the reaction to completion.) Finally, most of the organic liquid was decanted, the rest being separated from the residual salts by gentle filtration at the pump. The two solutions were mixed, dried over calcium chloride and the hydrazoic acid estimated by titration against standard potassium nitrite solution in the presence of sulphuric acid, with ferric chloride as indicator (see Gmelin, "Handbuch der Anorg. Chemie," Band 2B, p. 303, and Reith and Bouwman, *Pharm. Weekblad*, 1930, **67**, 475); yield of acid 80%.

The dry solution was placed in a 1-litre three-necked flask fitted with mechanical stirrer, dropping-funnel and water condenser. Anhydrous ferric chloride (1 g. for each gram of ketone) was added to the solution followed immediately by a few drops of *cyclo*hexanone. (Hydrazoic acid reacts slowly with benzene in the presence of ferric chloride, but more rapidly with *cyclo*hexanone.) The mixture was thoroughly cooled in ice, and 10 drops of ketone were added at intervals of 10 minutes until the calculated weight (3·8 mols.) had been added. The stirring was continued throughout the addition, and then for 15 hours subsequently during which time the temperature was allowed to rise as the ice melted. Nitrogen was evolved during the reaction and tended to carry away the volatile hydrazoic acid, but the condenser trapped some of this. The loss of hydrazoic acid probably accounts for the proportions recommended: 3·8 mols. of acid to 1 mol. of ketone. The resulting solution was made alkaline with 30% NaOH and filtered from the precipitated iron hydroxide. The benzene layer was separated and the aqueous layer saturated with ammonium sulphate. The aqueous layer was extracted six times with benzene (*ca.* 50 c.c. at a time). The united extracts were dried over sodium sulphate and the solvent distilled away under reduced pressure. The residual oil solidified on cooling and was first pressed on a porous porcelain to remove oily impurities, and then distilled at 203—204°/15 mm. or better at 150—153°/0·45 mm.

Sometimes the distillate was slightly yellow. This colour could be removed by crystallisation from a mixture of benzene–ligroin (80—100°). The tetrazole could also be crystallised from a large volume of ligroin. It had m. p. 58°; yield of distilled material 70%, yield of recrystallised material 50%. The identity of the substance was further established by the formation of the crystalline compound on the addition of saturated mercuric chloride solution (E.P. 257,418). "Cardiazol" is a trade mark of Messrs. Knoll Ltd.—UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, August 23rd*, 1945.]

The Preparation of 2-Amino-7-hydroxyfluorene. By. F. GOULDEN and GEORGE A. R. KON.

7-HYDROXY-2-ACETAMIDOFLUORENE has been isolated from the urine of animals treated with the carcinogenic compound 2-acetamidofluorene, and identified by synthesis (Bielschovsky, *Biochem. J.*, 1945, in the press). The method employed is not suitable for the preparation of large quantities because nitration of acetamidofluorene only gives small amounts of the required 7-nitro compound (Diels, Schill, and Tolson, *Ber.*, 1902, **35**, 3284) and the main product is the 3-isomeride. In our search for an improved method advantage was taken of the observation of Eckert and Langecker (*J. prakt. Chem.*, 1928, **226**, 263) that 2-aminofluorenone nitrates almost exclusively in position 7 and the purification of the resulting compound and its conversion into 7-nitro-2-hydroxyfluorenone present no difficulty. The latter compound is readily reduced to *7-amino-2-hydroxyfluorenone*. This compound or its *acetyl* derivative could not be converted into the corresponding fluorene by the Clemmensen method, but treatment with hydrazine and sodium ethoxide gave a quantitative yield of *7-amino-2-hydroxyfluorene*, which could then be acetylated to yield the product already prepared by Bielschovsky.

2-Aminofluorenone. 2-Nitrofluorenone (Diels, *Ber.*, 1901, **34**, 1758) was reduced as described by Eckert and Langecker (*loc. cit.*), the mixture being boiled for 7 hours. The yield of reprecipitated and recrystallised amino compound was 75%.

7-Nitro-2-aminofluorenone. The nitration of 2-aminofluorenone was carried out by the method of Eckert and Langecker, except that the amount of ice used for diluting the nitration mixture was reduced to one-third and sodium hydroxide used for the neutralisation; in this way 30 g. could conveniently be nitrated at once. Later, it was found preferable to omit the neutralisation and to isolate the nitroamino compound in the form of its sulphate, which separated as a solid when the nitration product was poured on to ice. It was suspended in hot water and at once decomposed with an excess of sodium hydroxide. The resulting dark brown solid, which should separate fairly easily, was washed with water and alcohol and dried at 100°. It was sufficiently pure for the next stage; it can be recrystallised from nitrobenzene.

7-Nitro-2-hydroxyfluorenone. The diazotisation of the nitroamino compound as described by Eckert and Langecker was readily carried out on a 30 g. scale; the mixture was poured on to ice and gradually heated to boiling; elimination of nitrogen was then complete. The phenol was readily isolated, but the purification was troublesome because the compound tends to precipitate in a finely divided form unless special precautions are taken. Attempts made to recrystallise it without reprecipitation were not satisfactory; it was found best to dissolve it in the minimum amount of 2N alkali (1 l.), filter the solution, diluting if necessary, and to heat it to boiling before adding excess of mineral acid. The solid (yield, 72—80%) was sufficiently pure for the next operation, but could be recrystallised from nitrobenzene.

7-Amino-2-hydroxyfluorenone.—The nitrohydroxy compound (20 g.) was boiled for 3 hours with AnalaR sodium sulphide (80 g.) and sodium hydroxide (40 g. in 1 l. of water). The solution was acidified with acetic acid, the solid separated, dissolved in dilute hydrochloric acid, filtered, made alkaline with sodium hydroxide, then again acidified with acetic acid. The brown solid (16·5 g.) was sufficiently pure for further treatment. It crystallised from nitrobenzene in brown needles, m. p. 235°, and was readily decomposed by heating its solution (Found: C, 73·8; H, 4·4. $C_{13}H_9O_2N$ requires C, 74·1; H, 4·3%). The *acetyl* compound was prepared by suspending the amine (1 g.) in water (75 c.c.), adding hydrochloric acid sufficient to dissolve the solid and shaking the filtered solution with acetic anhydride (2 c.c.) and an excess of sodium acetate. The lilac suspension was separated with difficulty, and the solid was purified through its sparingly soluble sodium salt; it crystallised from nitrobenzene in brick-red spear-shape crystals, m. p. above 310° (Found: C, 70·9; H, 4·6. $C_{15}H_{11}O_3N$ requires C, 71·1; H, 4·4%).

7-Amino-2-hydroxyfluorene.—Both nitrohydroxy- and aminohydroxy-fluorenone were rapidly reduced when 1 g. was boiled with amalgamated zinc filings (12·5 g.), acetic acid (32 c.c.), and hydrochloric acid (8 c.c.); the coloured solid in either case rapidly dissolved to a colourless solution; no crystalline compounds were isolated on dilution. Aminohydroxyfluorenone (1 g.) was heated overnight in a sealed tube with hydrazine hydrate (100%, 2 c.c.) and sodium ethoxide solution (5%, 16 c.c.) at 170°; higher temperatures should be avoided. The solution was diluted and acidified with acetic acid; *7-amino-2-hydroxyfluorene* was precipitated as a sandy powder (yield quantitative). It crystallised from anisole in small greenish-grey plates melting and decomposing indefinitely at about 260°; it was also easily decomposed by boiling its solution (Found: C, 78·9; H, 5·7. $C_{15}H_{11}O_3N$ requires C, 79·2; H, 5·6%). The acetyl compound was prepared from the crude reduction product by the procedure described above and after several crystallisations from 50% acetic acid formed small plates; m. p. and mixed m. p. 232°.

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