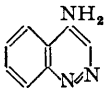
NOTES.

4-*Aminocinnoline*. By KINGSLEY BAKER.

No simple amino-derivatives of cinnoline have been described. 4-*Aminocinnoline* (I) has now been prepared by the action of alcoholic ammonia on 4-chlorocinnoline.


(I.)

4-Hydroxycinnoline (1 g.; Leonard and Boyd, *J. Org. Chem.*, 1946, **11**, 409) was refluxed with phosphorus oxychloride (5 ml.) for 30 minutes. The greater part of the unused reagent was removed by vacuum distillation, and the residue was poured on ice, made alkaline with sodium hydrogen carbonate, and extracted thrice with ether. The dried extract yielded 0·92 g. of crude 4-chlorocinnoline, m. p. *ca.* 60°. This was placed in a glass-lined steel tube with alcoholic ammonia (40 ml., saturated at − 8°) and copper acetate (trace) and heated in an oil-bath kept at 170° for 8 hours. The product was taken to dryness and extracted thrice with N-acetic acid. The acid extracts were treated with excess sodium hydroxide, giving 0·37 g. (39% yield, calculated on hydroxycinnoline) of pale yellow crystals, m. p. 208—210°, almost insoluble in cold water. Two recrystallisations from water produced 4-aminocinnoline as a light cream coloured microcrystalline powder, m. p. 209·5—210·5°, insoluble in ether, light petroleum, or benzene. It is sparingly soluble in boiling chlorobenzene with a gradient. The solutions show no fluorescence (Found: C, 65·7; H, 4·9; N, 28·7. $C_8H_7N_3$ requires C, 66·2; H, 4·9; N, 28·9%).

Unlike cinnoline itself, which is decomposed by air in a few minutes, this substance is quite stable and can be boiled with 2·5N-sodium hydroxide without loss of ammonia.

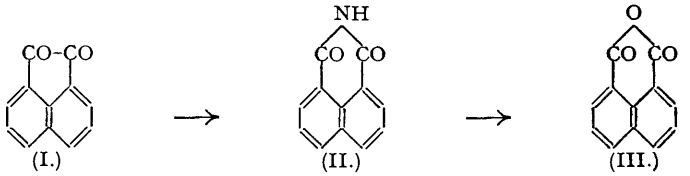
The author wishes to thank Dr. Adrien Albert for his interest and help, and Miss J. Fildes for the microanalysis.—UNIVERSITY OF SYDNEY. [*Received, October* 28th, 1947.]

Some Examples of the Schmidt Rearrangement. By W. G. H. EDWARDS and V. PETROW.

IN the course of other work we have had occasion to apply the Schmidt rearrangement (*Ber.*, 1924, **57**, 704; 1925, **58**, 2413) to a variety of compounds. The results, briefly outlined below, illustrate the highly specific character of this reaction.

Compounds containing a carbonyl grouping and a hetero-atom in the same ring in general failed to react. Experiments with oxindole, *N*-hydroxyoxindole, and 5-nitro-oxindole were not successful, the starting materials being recovered unchanged. *N*-Acetylindoxyl gave a dark amorphous solid which resisted all attempts at purification. Benz*iso*oxazolone and coumaranone were also recovered unchanged. The conversion of isatin into anthranilamide, reported by Caronna (*Gazzetta*, 1941, **71**, 585), has been confirmed and extended to the facile preparation of 4-chloro-, 6-chloro-, and 5-nitro-anthranilamides from the appropriate isatins. Isatin-7-carboxylic acid failed to react, a result which may be related to the depressed ketonic character of the β-carbonyl group owing to the proximity of the acid grouping.

Acenaphthenone gave a tarry product that could not be purified. Acenaphthenequinone (I) gave naphthalic anhydride (III), probably formed *via* (II) followed by hydrolysis by the sulphuric acid present in the reaction. An attempt to prepare the inaccessible 3-aminoacenaphthene from 3-acetylacenaphthene, readily obtained by the method of Fieser and Hershberg (*J. Amer. Chem. Soc.*, 1939, **61**,


(I.) (II.) (III.)

1278), gave a mixture of 3-amino- and 3-acetamido-acenaphthenesulphonic acid. The relationship between the two compounds was demonstrated by acetylation of the former to a product whose S-*benzyl*iso*thiouronium* salt proved identical with that of the latter acid. 3-Acetamidoacenaphthene, it may be added, has been found to undergo rapid sulphonation in concentrated sulphuric acid at 0°. Attempts to carry out the rearrangement in syrupy phosphoric acid failed, unchanged ketone being recovered.

Experimental.—Melting points are corrected. Semi-microanalyses are by Mr. S. Bance, B.Sc., A.R.I.C., Analytical Division, May and Baker Ltd.

The Schmidt rearrangements were carried out as follows. A solution of the compound in 10 vols. of concentrated sulphuric acid at 0° was treated with 1·1 equivs. of sodium azide, dissolved in the minimum quantity of distilled water and added dropwise with stirring over a period. After standing overnight, the mixture was poured on 10 times its weight of crushed ice, neutralised as necessary, and the product collected and purified.

5-Nitroanthranilamide, obtained by neutralisation of the product from the Schmidt rearrangement, formed orange needles from water (42%), m. p. 236° (Found: C, 46·5; H, 4·0; N, 23·5. Calc. for $C_7H_7O_3N_3$: C, 46·5; H, 3·9; N, 23·1%).

4-Chloroanthranilamide, prepared from 6-chloroisatin, formed prisms from ethanol (80%), m. p. 181° (Found: C, 49·5; H, 4·1; N, 16·3; Cl, 20·8. Calc. for $C_7H_7ON_2Cl$: C, 49·3; H, 4·1; N, 16·4; Cl, 20·8%), not depressed in admixture with an authentic specimen. The latter was obtained by the action of ammonia (5 ml.; *d* 0·88) on methyl 4-chloro-2-aminobenzoate (1 g.) in a sealed tube for 16 hours at 100—110°, m. p. 181° (Found: C, 49·5; H, 4·3; N, 16·5%). 4-Chloroisatin gave 6-chloroanthranilic acid (40%), colourless plates from benzene, m. p. 132°.

3-*Acetylacenaphthene experiments.* 3-Acetylacenaphthene (5 g.) in concentrated sulphuric acid (50 ml.) at 0° was treated with stirring with sodium azide (1·85 g.) in water (7·5 ml.). After 2 hours, ice (50 g.) was added, and the mixture filtered and washed with water (15 ml.); unchanged ketone (600 mg.) was then recovered. On mixing the filtrate and washings, a buff crystalline solid (2·1 g.) was deposited. It was collected, washed with acetone, and identified as 3-acetamidoacenaphthenesulphonic acid by conversion into the S-*benzylisothiouronium* salt, needles from 50% ethanol, m. p. 226° (decomp.) (Found: C, 55·8; H, 5·3; N, 8·9; S, 13·8. $C_{22}H_{33}O_4N_3S_2,H_2O$ requires C, 55·7; H, 5·3; N, 8·9; S, 13·5%). The acid filtrates (above) deposited a buff solid (900 mg.) on standing, which was evidently the 3-aminoacenaphthenesulphonic acid, as after acetylation it gave the same *S*-benzyl*iso*thiouronium salt, m. p. 226°.

The authors thank Dr. A. J. Ewins, D.Sc., F.R.S., and the Directors of Messrs. May and Baker Ltd. for research facilities generously placed at the disposal of one of them (W. G. H. E.).—May and Baker Ltd., Dagenham. Queen Mary College (University of London), E. 1. [*Received, October 30th,* 1947.]

The Preparation of 4 : 4′-*Diamino- and* 4 : 4′-*Dihydroxy*-2 : 2′-*dinaphthyl.* By Herbert H. Hodgson and Stanley Dixon.

The initial material for these preparations was the 4 : 4′-dinitro-2 : 2′-dinaphthyl prepared by Hodgson and Elliott (*J.*, 1937, 123) by the action of precipitated copper powder on 3-iodo-1-nitronaphthalene in nitrobenzene solution.

Reduction of 4 : 4′-*Dinitrodinaphthyl.*—A mixture of finely sieved 4 : 4′-dinitro-2 : 2′-dinaphthyl (10 g.), glacial acetic acid (100 c.c.), and hydrochloric acid (20 c.c., *d* 1·18) was reduced at the boil until colourless by the gradual addition of zinc dust (20 g.). During the reduction a heavy white precipitate of a zinc chloride double compound separated. After being cooled and diluted with water, the mixture was treated with aqueous sodium hydroxide in sufficient amount to dissolve all the zinc hydroxide. The precipitated 4 : 4′-*diamino*-2 : 2′-*dinaphthyl* was filtered off, and the filtrate extracted with chloroform to recover a small amount in solution; yield, 6·5 g. (78·7%). The diamine crystallised from a mixture of chloroform and light petroleum in white needles, m. p. 131° (Found: N, 9·7. $C_{20}H_{16}N_2$ requires N, 9·86%); it was only very sparingly soluble in water, but soluble in all the more common organic solvents except light petroleum, in which it was almost insoluble. The *dihydrochloride* was obtained in colourless needles by addition of hydrochloric acid (*d* 1·18) to a solution of the diamine in glacial acetic acid; it was almost completely insoluble in water; m. p. 308° (Found: HCl, 19·9. $C_{20}H_{16}N_2,2HCl$ requires HCl, 20·4%).

4 : 4′-*Diacetamido*-2 : 2′-*dinaphthyl* was formed when the diamine (0·5 g.) was heated with acetic anhydride (10 c.c.) on the water-bath for 15 minutes. On cooling, the diacetyl compound crystallised out and was all recovered (0·6 g., 92% yield) by dilution with water; it crystallised from glacial acetic acid in colourless needles, m. p. 340° (Found: N, 7·4. $C_{24}H_{20}O_2N_2$ requires N, 7·6%).

4 : 4′-*Dibenzamido*-2 : 2′-*dinaphthyl* was formed when the diamine was dissolved in pyridine (10 c.c.) and the solution heated with benzoyl chloride (0·8 g.) on the water-bath for 30 minutes, then diluted with water, and the separated benzoyl derivative filtered off, dried, and crystallised from nitrobenzene from which it separated (0·65 g., 75% yield) in colourless needles, m. p. 319° (Found: N, 5·5. $C_{34}H_{24}O_2N_2$ requires N, 5·7%).

4 : 4′-*Bistoluene*-p-*sulphonamido*-2 : 2′-*dinaphthyl* was formed when the solution of the diamine (0·5 g.) in pyridine (10 c.c.) was heated at the boil for 15 minutes with toluene-*p*-sulphonyl chloride (1·2 g.), then cooled, diluted with water, and the tarry precipitate hardened by washing it with dilute hydrochloric acid; the compound crystallised from nitrobenzene in colourless needles, m. p. 289° (Found: N, 4·5. $C_{34}H_{28}O_4N_2S_2$ requires N, 4·7%), in a yield of 0·8 g. (75·5%).

Preparation of 4 : 4′-*Dihydroxy*-2 : 2′-*dinaphthyl.*—A solution of 4 : 4′-diamino-2 : 2′-dinaphthyl (5 g.) in glacial acetic acid (15 c.c.) was stirred vigorously into 10% aqueous sulphuric acid (150 c.c.) to obtain a fine suspension of the insoluble sulphate. The mixture was cooled with ice and diazotised at 0° by the addition of a solution of sodium nitrite (2·45 g.) in water (50 c.c.). The diazo-solution was filtered, and the filtrate gradually raised to the boil; a vigorous evolution of nitrogen occurred, and 4 : 4′-*dihydroxy*-2 : 2′-*dinaphthyl* was precipitated. When the decomposition was complete, the precipitate was filtered off and extracted with hot 5% aqueous sodium hydroxide to remove the dihydroxy-compound, which was reprecipitated from the filtered extract by addition of acid, removed by

filtration, washed until acid-free, and recrystallised from 50% aqueous methanol. It formed colourless plates, m. p. 217° (Found : C, 83·8; H, 4·8. $C_{20}H_{14}O_2$ requires C, 83·9; H, 4·9%); yield, 3·8 g. (77%).

The authors thank Imperial Chemical Industries Ltd., Dyestuffs Division, for gifts of chemicals.—
TECHNICAL COLLEGE, HUDDERSFIELD. [*Received, November 3rd*, 1947.]

The Condensation of p-*Dimethylaminobenzaldehyde with* 4-*Methylpyrimidine Derivatives*. By D. M. BROWN and W. C. J. ROSS.

Ross (this vol., p. 1128) reported an unsuccessful attempt to prepare 4-styryl derivatives of uracil. When 4-methyluracil was heated with benzaldehyde or *p*-nitrobenzaldehyde in the presence of zinc chloride, condensation probably occurred at the 5-position in the pyrimidine nucleus with the formation of a xanthine-like compound; however, 5-nitro-4-methyluracil readily condensed with these aldehydes to give the required styryl derivatives. When dimethylaminobenzaldehyde was heated with 4-methyluracil in the presence of zinc chloride no definite product was obtained, but when they were heated together in aniline solution 4-(p-*dimethylaminostyryl*)*uracil* was formed. This method of condensation does not appear to have been used previously for the preparation of styrylpyrimidines. The reaction involves the elimination of aniline between the anil of the aldehyde and methyluracil, and when this anil was heated with 4-methyluracil at 180° the same condensation product was obtained, but it was more convenient to carry out the reaction as described below. Benzaldehyde did not condense with 4-methyluracil under these conditions. Chlorination of 4-(*p*-dimethylaminostyryl)uracil using phosphorus oxychloride afforded 2 : 6-*dichloro*-4-(p-*dimethylaminostyryl*)*pyrimidine*; this did not react with a solution of ammonia in methanol at the boiling point of the solvent, but at 150° a *chloro-amino*-derivative was formed. An attempt to prepare 6-chloro-2-amino-4-(*p*-dimethylaminostyryl)pyrimidine for comparison with this monoamine was unsuccessful, since neither 2-amino-6-hydroxy-4-methylpyrimidine nor the corresponding 6-chloro-derivative could be condensed with *p*-dimethylaminobenzaldehyde. 2-Thio-4-methyluracil condensed with *p*-dimethylaminobenzaldehyde in aniline solution to give 2-*thio*-4-(p-*dimethylaminostyryl*)*uracil*, and 6-hydroxy-4-methylpyrimidine similarly reacted to give 6-*hydroxy*-4-(p-*dimethylaminostyryl*)*pyrimidine*. Chlorination of the last compound yielded 6-*chloro*-4-(p-*dimethylaminostyryl*)*pyrimidine*, and this reacted with piperidine to give 6-*piperidino*-4-(p-*dimethylaminostyryl*)*pyrimidine*.

4-(p-*Dimethylaminostyryl*)*uracil*.—4-Methyluracil (25 g.), *p*-dimethylaminobenzaldehyde (50 g.), and aniline (400 c.c.) were heated under reflux for 24 hours. The water formed at the start of the reaction was removed by distillation. The cooled mixture was diluted with an equal volume of methanol, and the solid which separated washed with methanol and then ether (11·4 g. of amorphous material). The product was obtained in small yellow plates by dissolving it in hot acetic acid and then diluting with methanol; m. p. 325—330°, after a second crystallisation (Found : C, 65·0; H, 5·7; N, 16·6. $C_{14}H_{15}O_2N_3$ requires C, 65·4; H, 5·9; N, 16·3%). The compound exhibits a yellow-green fluorescence in ultra-violet light.

2 : 6-*Dichloro*-4-(p-*dimethylaminostyryl*)*pyrimidine*.—4-(*p*-Dimethylaminostyryl)uracil (1·5 g.) was heated under reflux with phosphorus oxychloride (9 c.c.) for 20 minutes. The mixture was poured on ice (100 g.) and extracted with ether, giving a yellow-green fluorescent solution from which orange crystals (0·75 g.) separated on evaporation. After recrystallisation from methanol, the *dichloro*-compound formed long flattened orange needles, m. p. 181—183° (Found : C, 57·0; H, 4·5. $C_{14}H_{13}N_3Cl_2$ requires C, 57·2; H, 4·5%).

Action of Ammonia on the Dichloro-compound.—The dichloro-compound (1·5 g.) was heated for 4 hours in a sealed tube at 140—150° (glycerol-bath temperature) with a solution of ammonia in methanol (30 c.c., saturated at room temperature). The orange solid gradually passed into solution, and later pale yellow crystals of the *monoamino*-compound separated from the hot solution. The product, after being washed with methanol, decomposed on heating and finally melted above 270° (Found : C, 61·4; H, 5·5. $C_{14}H_{15}N_4Cl$ requires C, 61·2; H, 5·5%).

2-*Thio*-4-(p-*dimethylaminostyryl*)*uracil*.—2-Thio-4-methyluracil (1·0 g.), *p*-dimethylaminobenzaldehyde (1·0 g.), and aniline (15 c.c.) were heated under reflux for 4 hours, and then the cooled mixture was diluted with an equal volume of methanol. The orange-red solid which separated was dissolved in dilute hydrochloric acid. The colourless solution was warmed and then saturated with sodium acetate. The *thio*-derivative which separated was washed well with warm water and finally with methanol. After being dried at 140°/0·001 mm. the compound decomposed above 280° without melting (Found : C, 61·6; H, 5·8. $C_{14}H_{15}ON_3S$ requires C, 61·5; H, 5·5%).

6-*Hydroxy*-4-(p-*dimethylaminostyryl*)*pyrimidine*.—6-Hydroxy-4-methylpyrimidine was liberated from the hydriodide (Gabriel and Colman, *Ber.*, 1899, **32**, 2930) by treatment of the aqueous solution with lead acetate. The free base (3·3 g.), *p*-dimethylaminobenzaldehyde (4·5 g.), and aniline (6 c.c.) were heated under reflux for 4 hours. The dark solution was cooled and diluted with methanol (6 c.c.). The *product* (0·9 g.) separated from acetic acid–methanol as a yellow crystalline powder, m. p. 295—297° (Found : C, 69·4; H, 6·2. $C_{14}H_{15}ON_3$ requires C, 69·7; H, 6·3%).

6-*Chloro*-4-(p-*dimethylaminostyryl*)*pyrimidine*.—The above hydroxy-compound (1·2 g.) and phosphorus oxychloride (6 c.c.) were heated under reflux for 1½ hours. The mixture was poured on ice and the solution was then basified with ammonia and extracted with benzene. After drying, the benzene solution was percolated down a column of activated alumina. Elution of the yellow band with more benzene followed by the evaporation of the solvent gave the *chloro*-compound which separated from benzene–light petroleum (b. p. 60—80°) in the form of yellow leaflets (0·3 g.), m. p. 192° (Found : C, 64·7; H, 5·5. $C_{14}H_{14}N_3Cl$ requires C, 64·7; H, 5·4%).

6-*Piperidino*-4-(p-*dimethylaminostyryl*)*pyrimidine*.—The chloro-compound (100 mg.) and piperidine (0·5 c.c.) were heated at the boiling point for 5 minutes. After the addition of water an oil separated. This solidified on standing, and was then washed, dried, and recrystallised from light petroleum (b. p.

60—80°), giving small pale yellow needles (75 mg. after two crystallisations), m. p. 126° (Found: C, 74·5; H, 7·6. $C_{19}H_{24}N_4$ requires C, 74·0; H, 7·8%).

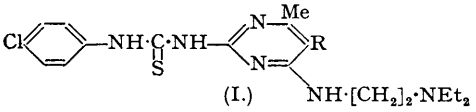
This investigation has been supported through grants made to the Royal Cancer Hospital (Free) by the British Empire Cancer Campaign, the Anna Fuller Fund, and the Jane Coffin Childs Memorial Fund. One of us (W. C. J. R.) wishes to thank the Sir Halley Stewart Trust for the award of a research Fellowship.—The Chester Beatty Research Institute, The Royal Cancer Hospital (Free), Fulham Road, London, S.W. 3. [*Received, November 20th*, 1947.]

Symmetrically Disubstituted Formamidines. Formation by Raney-nickel Reduction of Thioureas.

By R. deBrath Ashworth.

The use of Raney nickel alone (*i.e.*, in the absence of added hydrogen) as a reducing agent has been described by Mozingo (*J. Amer. Chem. Soc.*, 1943, **65**, 1013), who converted benzoylmethionine into α-benzamidobutyric acid, and more recently Wolfram and Karabino (*ibid.*, 1944, **66**, 909) have used this reagent for the reduction of thioacetals to the corresponding methylenic compounds. After the completion of the work now described a paper by Cattelain and Chabrier (*Bull. Soc. chim.*, 1940, **6**, 781) became available in which the reduction of certain monosubstituted thioureas by Raney nickel was described; *e.g.*, benzylthiourea yielded ammonia, methylamine, and toluene, whereas sodium α-mercaptocinnamate afforded β-phenylpropionic acid. There appeared to be no literature reference, however, to the reduction of *s*-disubstituted thioureas to formamidines.

The work described here was carried out on compounds of type (I) which were available as a result of an earlier antimalarial research (Ashworth, Crowther, Curd, and Rose, *J.*, this vol., p. 581). By reduction



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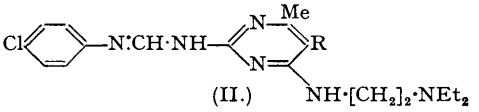


(II.)

of 4-2′-diethylaminoethylamino-2-*p*-chlorophenylthioureido-6-methylpyrimidine (I; R = H) with Raney nickel in cold ethyl acetate there was obtained a high yield of a compound $C_{18}H_{25}N_6Cl$, to which the structure (II; R = H) was assigned. To check the course of the reduction, thiocarbanilide was used as a model substance and under identical conditions gave a good yield of diphenylformamidine. The ultra-violet absorption spectrum of the new compound (II; R = H) shows a maximum at 2920 A., and the urea corresponding to (I; R = H) (Ashworth *et al.*, *loc. cit.*) shows a maximum at 2510 A., and this shift in the maximum is considered to be due to the introduction of a double bond into the molecule, most probably in conjugation with the phenyl nucleus.

Reduction of *p*-chlorophenylthiourea gave an unidentified basic liquid and no uniform product could be isolated from the attempted reduction of *N*-amidino-*N′*-*p*-chlorophenylthiourea. However, the Raney nickel reduction of 4-2′-diethylaminoethylamino-2-*p*-chlorophenylthioureido-6-methyl-5-ethylpyrimidine (I; R = Et) and of 2-*p*-chlorophenylthioureido-4 : 6-dimethoxypyrimidine gave the corresponding formamidines (II; R = Et) and *N′*-*p*-chlorophenyl-*N*-(4 : 6-dimethoxy-2-pyrimidyl)-formamidine, respectively.

Experimental.—N′-p-*Chlorophenyl*-N-(4-2′-*diethylaminoethylamino*-6-*methyl*-2-*pyrimidyl*)*formamidine* (II; R = H). 4-2′-Diethylaminoethylamino-2-*p*-chlorophenylthioureido-6-methylpyrimidine (9 g.) in ethyl acetate (40 c.c.) was shaken for 15 hours with Raney nickel (37 g. of alcoholic paste) at room temperature. The mixture was then raised to the boil, filtered, and allowed to cool. The crystalline *product* was collected, and the filtrate used to re-extract the nickel, a further small quantity being thus obtained (yield, 5·2 g.). After recrystallisation from ethyl acetate it had m. p. 174—175° (Found: C, 60·0, 59·8; H, 7·0, 7·0; N, 23·3. $C_{18}H_{25}N_6Cl$ requires C, 60·0; H, 6·95; N, 23·3%). The yield was not improved by the continuous passage of hydrogen through the solution, and the use of alcohol as solvent gave an impure product. No reduction occurred with palladium and hydrogen, and reduction with zinc dust and ammonium chloride gave a non-characterisable product.

NN′-*Diphenylformamidine*. *NN′*-Diphenylthiourea (5 g.) in ethyl acetate (20 c.c.) was treated with Raney nickel (20 g.) as in the preceding experiment. The product obtained by evaporating the ethyl acetate to dryness under dimished pressure was crystallised from light petroleum (b. p. 60—80°)–alcohol and then had m. p. 137—138° undepressed in admixture with authentic *NN′*-diphenylformamidine (Found: C, 79·2; H, 5·8; N, 14·5. Calc. for $C_{13}H_{12}N_2$: C, 79·6; H, 6·1; N, 14·3%).

N′-p-*Chlorophenyl*-N-(4-2′-*diethylaminoethylamino*-6-*methyl*-5-*ethyl*-2-*pyrimidyl*)*formamidine* (II; R = Et). 4-2′-Diethylaminoethylamino-2-*p*-chlorophenylthioureido-6-methyl-5-ethylpyrimidine (1 g.) was dissolved in ethyl acetate (8 c.c.) and shaken with Raney nickel (7·5 g. of alcoholic paste) and worked up as described above to give the *product* (yield, 0·2 g.), which had m. p. 149—151° after recrystallisation from light petroleum (b. p. 80—100°) (Found: C, 61·4; H, 7·2; N, 21·4. $C_{20}H_{29}N_6Cl$ requires C, 61·7; H, 7·3; N, 21·6%).

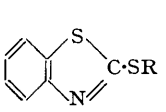
N′-p-*Chlorophenyl*-N-(4 : 6-*dimethoxy*-2-*pyridyl*)*formamidine*. 2-*p*-Chlorophenylthioureido-4 : 6-dimethoxypyrimidine (to be described in a forthcoming communication) (8·5 g.) was reduced in the usual way in ethyl acetate (70 c.c.) with Raney nickel (52·5 g. of alcoholic paste). The *product* (3·5 g.) was purified by crystallisation from alcohol and then had m. p. 178—179·5° (Found: C, 53·6; H, 4·5. $C_{13}H_{13}O_2N_4Cl$ required C, 53·3; H, 4·45%).

The author wishes to thank Dr. F. S. Cropper for the spectroscopic data and Dr. F. H. S. Curd for advice.—Imperial Chemical Industries Ltd., Research Laboratories, Blackley, Manchester, 9. [*Received, December 4th*, 1947.]

The Hydroxymethyl Derivative of 2-Mercaptobenzthiazole. By W. A. SEXTON and A. SPINKS.

2-MERCAPTOBENZTHIAZOLE and aqueous or alcoholic formaldehyde afford a hydroxymethyl derivative to which the structure 2-hydroxymethylthiobenzthiazole has been assigned (B.P. 361,971; Levi, *Gazzetta*, 1932, **62**, 775). The *S*-substituted structure has also been assumed for various derivatives such as the condensation products of 2-mercaptobenzthiazole with formaldehyde and amines (B.PP. 377,253, 410,454) and with formaldehyde and β-naphthol (B.P. 476,838), the reaction products of the hydroxymethyl compound with acyl halides and phenyl *iso*cyanate (B.P. 475,220), the condensation product of 2-mercaptobenzthiazole with "dimethylolurea" (bishydroxymethylurea) (B.P. 470,791) and the chloromethyl compound obtained with phosphorus trichloride (B.P. 475,221).

Although methylation of the thiol compound (I; R = H) with methyl sulphate and methyl iodide affords only a small proportion of the *N*-methyl derivative (II; R = Me) (Reed, Robertson, and Sexton, *J.*, 1939, 473), the facts that (i) 2-mercaptobenzthiazole shows in solution the structure (II; R = H) (Morton and Stubbs, *J.*, 1939, 1321), and (ii) the hydroxymethyl derivative is formed in the absence of alkali, caused us to question the hitherto accepted structure. We have therefore investigated the ultraviolet absorption spectra of the hydroxymethyl and the piperidinomethyl derivative of 2-mercaptobenzthiazole, and a comparison with the data provided by Morton and Stubbs (*loc. cit.*) shows clearly that they possess *N*-substituted structures (II; R = CH_2·OH and R = CH_2·NC_5H_{10}, respectively). The structures of the various derivatives described in the patents mentioned above therefore require appropriate modification.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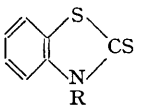

(II.)

2-Thio-3-hydroxymethylbenzthiazolone (II; R = CH_2·OH).—2-Mercaptobenzthiazole (34 g.) was boiled for 1¾ hours with alcohol (30 c.c.) and 37% formaldehyde (20 g.). On cooling, the crystalline product (33·7 g.) was separated, washed with 50% alcohol, and recrystallised from toluene (charcoal); m. p. 129—130° (Levi, *loc. cit.*, gives m. p. 125—130° for his "2-hydroxymethylthiobenzthiazole") (Found: N, 7·1; S, 32·15. $C_8H_7ONS_2$ requires N, 7·1; S, 32·5%). The *compound* resembles 2-thio-3-methylbenzthiazolone in its insolubility in concentrated hydrochloric acid. It is decomposed by boiling water and by cold dilute sodium hydroxide with regeneration of 2-mercaptobenzthiazole.

2-Thio-3-piperidinomethylbenzthiazolone (II; R = CH_2·NC_5H_{10}).—Piperidine (8·5 g.) was mixed with 37% formaldehyde (8·3 g.) and to the cooled mixture was added 2-mercaptobenzthiazole (16·7 g.) dissolved in acetone (80 c.c.). The yellow crystalline *compound* was separated and recrystallised; yellow prisms from ethyl acetate, m. p. 154—156°; B.P. 377,253 gives m. p. 159—161° for the alternative structure (Found: N, 10·2; S, 24·2. $C_{13}H_{16}N_2S_2$ requires N, 10·3; S, 24·3%).

2-Thio-3-chloromethylbenzthiazolone (II; R = CH_2Cl).—The foregoing hydroxymethyl compound (19·7 g.) was mixed with phosphorus trichloride (8·5 c.c.). After the initial vigorous reaction had subsided, ethylene chloride (25 c.c.) was added, and the mixture boiled for 20 minutes. The hot solution was decanted from gummy material, and the crystalline product which separated on cooling was recrystallised from benzene; pale yellow needles, m. p. 127—128°; B.P. 475,221 gives m. p. 127—128° for the supposed isomer (Found: S, 29·7; Cl, 16·2. $C_8H_6NClS_2$ requires S, 29·7; Cl, 16·5%). This *compound* contains a reactive halogen atom and tends to deteriorate in moist air.

Absorption Spectra.—These were determined in methyl-alcoholic solution, a Beckmann spectrophotometer being used. The values of the principal absorption bands are given below in comparison with those found by Morton and Stubbs (*loc. cit.*) for 2-mercaptobenzthiazole and its isomeric methyl derivatives. The general shape of the curves for the two new compounds and the position of the maxima showed such close agreement with those for (II; R = H or Me) that there was no doubt as to the essential identity of the absorbing system. A minor point was the failure to observe with our compounds the resolution of the band at λ = 236 mμ as recorded by Morton and Stubbs for (II; R = Me).

Compound.	$\lambda_{max.}$	log $\epsilon_{max.}$	Compound.	$\lambda_{max.}$	log $\epsilon_{max.}$
(II; R = H)	325	4·43	(II; R = Me)	324·5	4·41
	235	4·10		241	4·14
(II; R = CH_2·OH)	321	4·34		231	4·13
	236	4·41	(I; R = Me)	300·5	3·92
(II; R = CH_2·NC_5H_{10})	323	4·39		280	4·09
	236·5	4·14		224	4·36

The absorption of the chloromethyl compound in the same solvent was not determined owing to the reactivity of the halogen atom.—RESEARCH LABORATORIES, IMPERIAL CHEMICAL INDUSTRIES LTD., BLACKLEY, MANCHESTER. [*Received, December 9th*, 1947.]

Derivatives of 2 : 4-Dinitrophenylacetone. By J. S. MORLEY, J. C. E. SIMPSON, and O. STEPHENSON.

2 : 4-DINITROPHENYLACETONE, originally prepared from ethyl 2 : 4-dinitrophenylacetoacetate (Borsche, *Ber.*, 1909, **42**, 601), was also readily obtained from 2 : 4-dinitrophenylacetyl chloride and ethyl ethoxymagnesiomalonate (cf. Walker and Hauser, *J. Amer. Chem. Soc.*, 1946, **68**, 1386). Reduction yielded a nitro-amine which is probably *4-nitro-2-aminophenylacetone*, as diazotisation yielded a sparingly soluble

product which was not a diazonium salt but was possibly the related indazole. 2 : 4-Dinitrophenylacetoxime on reduction gave a product which diazotised normally but showed no tendency to cyclise to a dihydrocinnoline, and is therefore probably the *oxime* of 2-nitro-4-aminophenylacetone.

Condensation of 2-chloro-3 : 5-dinitrobenzoic acid with ethyl acetoacetate by the method of Borsche (*loc. cit.*) yielded *ethyl* 2 : 4-*dinitro*-6-*carboxyphenylacetoacetate* (I), from which the arylacetone could not be prepared by fission with concentrated sulphuric acid (Borsche, *loc. cit.*) or by other means. Treatment of (I) with acetic anhydride and with phenylsemicarbazide gave *products*, m. p. 124° and 256° respectively, and interaction of (I) and hydroxylamine yielded two *products*, m. p. 230° and 239°. The structures of these four products are unknown.

Contrary to the claim of Brown and Campbell (*J.*, 1937, 1699), 2 : 4-dinitrobenzoic acid could not be prepared by simultaneous nitration and oxidation of phenylacetic acid; several repetitions of their work gave 2 : 4-dinitrophenylacetic acid in good yield as the sole isolable product.

2 : 4-*Dinitrophenylacetic Acid.*—The reaction of phenylacetic acid with nitric acid (*d* 1·5) was carried out exactly as described by Brown and Campbell (*loc. cit.*), and also with longer periods of reflux (3 hours) and with more concentrated nitric acid (*d* 1·53). In each case the acid had m. p. 181—182° (efferv.) [Borsche (*Ber.*, 1909, **42**, 1310) gives m. p. 179° (decomp.)], unchanged by crystallisation from aqueous alcohol (150—154° when mixed with 2 : 4-dinitrobenzoic acid, m. p. 181—182°, prepared from 2 : 4-dinitrophenyl cyanide).

2 : 4-*Dinitrophenylacetone.*—The acid prepared as above (21 g.), phosphorus pentachloride (23 g.), and benzene (40 c.c.) were heated under reflux for ½ hour, and phosphorus oxychloride removed by repeated evaporation with benzene under reduced pressure. A solution of the residue in ether (200 c.c.) was added dropwise to a stirred solution prepared from magnesium (2·68 g.), ethyl malonate (17·6 g.), alcohol (12·5 c.c.), ether (50 c.c.), and carbon tetrachloride (0·25 c.c.). After ½ hour (reflux) the mixture was cooled and acidified (sulphuric acid), and the product was collected with ether, freed from solvent, and refluxed for 5 hours with a mixture of glacial acetic acid (30 c.c.), concentrated sulphuric acid (3·8 c.c.), and water (20 c.c.). Partial neutralisation of the ice-cold solution gave almost pure 2 : 4-dinitrophenylacetone (12·3 g.), m. p. 77—78° alone and mixed with authentic material (Borsche, *Ber.*, 1909, **42**, 601) after crystallisation from ether–ligroin (Found: C, 48·1; H, 3·75; N, 12·4. Calc. for $C_9H_8O_5N_2$: C, 48·2; H, 3·6; N, 12·5%).

4-*Nitro*-2-*aminophenylacetone.*—A suspension of the dinitro-ketone (0·84 g.) in alcohol (5 c.c.) and concentrated hydrochloric acid (1 c.c.) was treated during ¼ hour at 20—25° with a solution of stannous chloride (2·8 g.) in concentrated hydrochloric acid (5 c.c.). After 5 minutes at 30—35°, the clear red solution was diluted with water (5 c.c.), and the precipitated *amine* (0·44 g., m. p. 159—160°) recrystallised from water containing a drop of hydrochloric acid, from which it separated in long, silky orange needles, m. p. 161—162° (decomp.) (Found: C, 56·2; H, 4·7; N, 14·7. $C_9H_{10}O_3N_2$ requires C, 55·7; H, 5·2; N, 14·4%). The amine was prepared from the dinitro-ketone obtained from 2 : 4-dinitrophenylacetic acid and also from ethyl 2 : 4-dinitrophenylacetoacetate; it gave a red colour in very weakly alkaline, but was stable in faintly acid, solutions.

Oxime of 2-*Nitro*-4-*aminophenylacetone.*—A finely-divided suspension of 2 : 4-dinitrophenylacetoxime (2 g.) (Borsche, *Annalen*, 1912, **390**, 25) in alcohol (100 c.c.) and water (150 c.c.) was shaken for 1 hour with aqueous sodium hydrogen sulphide (from 0·7 g. of sodium hydroxide in 40 c.c. of water); the mixture was then heated on the water-bath until a clear red solution was obtained, and this was left at room temperature for 2 days. The *nitro-amine* which had then separated (0·57 g.) was crystallised from methanol, giving yellow needles, m. p. 205°, easily soluble in dilute mineral acids and in excess of sodium hydroxide (Found: C, 52·0; H, 5·1. $C_9H_{11}O_3N_3$ requires C, 51·65; H, 5·3%).

Ethyl 2 : 4-*Dinitro*-6-*carboxyphenylacetoacetate.*—A solution of ethyl acetoacetate (52 g.) in ether (350 c.c.) was treated with sodium (9·2 g.) followed by methyl alcohol (50 c.c.). A solution of 2-chloro-3 : 5-dinitrobenzoic acid (25 g.) in methyl alcohol (50 c.c.) and ether (250 c.c.) was added, and the whole heated under reflux for 3—4 hours. The solution was then washed with water and very dilute sodium hydroxide solution, the combined washings made acid to Congo-red, and the product crystallised (aqueous methanol, benzene–ligroin, and finally benzene); the *ester* (14—15 g.) separated in small colourless needles, m. p. 142—143°, giving a deep red colour with alcoholic ferric chloride (Found: C, 46·4; H, 3·6; N, 8·6. $C_{13}H_{12}O_9N_2$ requires C, 45·9; H, 3·55; N, 8·2%), easily soluble in aqueous sodium acetate and in methyl alcohol, moderately in benzene, and very sparingly in ligroin.

Reactions of Ethyl 2 : 4-*Dinitro*-6-*carboxyphenylacetoacetate.*—(*a*) The ester (0·75 g.) and acetic anhydride (1 g.) were refluxed for 10 minutes, solvent removed (reduced pressure), and the residue crystallised from ether and finally from ether–ligroin, from which the *product* separated in colourless crystals, m. p. 124° with previous softening, insoluble in dilute sodium carbonate (Found: C, 47·3; H, 3·1; N, 9·0. $C_{13}H_{10}O_8N_2$ requires C, 48·4; H, 3·1; N, 8·7%).

(*b*) The ester (0·2 g.) and phenylsemicarbazide (0·1 g.) were refluxed for ¾ hour in alcohol (6 c.c.) containing acetic acid (4 drops). After slight concentration, the solution was diluted with water (2 vols.), and the precipitated solid recrystallised from alcohol and finally from aqueous acetic acid, from which the *product* separated in fine yellow needles, m. p. 255—256° (decomp.) (Found: C, 52·7; H, 3·8; N, 15·5. $C_{20}H_{17}O_8N_5$ requires C, 52·7; H, 3·75; N, 15·4%).

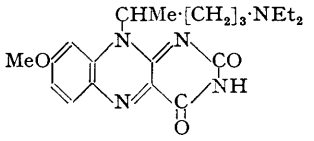
(*c*) A solution of the ester (3 g.), hydroxylamine hydrochloride (3 g.), and sodium acetate crystals (6 g.) in alcohol (35 c.c.) and water (100 c.c.) was heated under reflux for 4 hours, cooled, diluted with water, and made just acid to Congo-red with hydrochloric acid. The solid which separated was recrystallised from benzene–alcohol, yielding a *substance* which formed bright yellow needles, m. p. 239° (Found: C, 45·25; H, 2·8; N, 15·7. $C_{10}H_7O_6N_3$ requires C, 45·3; H, 2·65; N, 15·85%). The aqueous filtrate from this substance was extracted with ether; evaporation of the washed and dried extract yielded a second *substance*, sparingly soluble in benzene, which, after several crystallisations from benzene–alcohol, formed pale yellow needles, m. p. 230° (decomp.) (220° when mixed with the foregoing compound); it gave brownish-yellow solutions in alcohol and acetone, almost colourless in benzene, and deep red in aqueous or alcoholic sodium hydroxide (Found: C, 42·6; H, 2·3. $C_{11}H_7O_8N_3$ requires C, 42·7; H, 2·3%).

We are indebted to the Medical Research Council for a Research Studentship (J. S. M.).—DURHAM COLLEGES IN THE UNIVERSITY OF DURHAM. WARRINGTON YORKE DEPARTMENT OF CHEMOTHERAPY, LIVERPOOL SCHOOL OF TROPICAL MEDICINE. [*Received, December 12th,* 1947.]

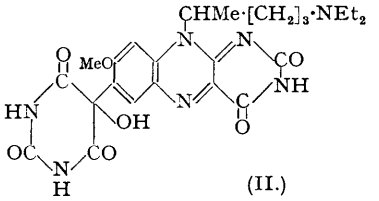
Contribution to the Chemistry of Synthetic Antimalarials. Part VII. The Reaction between Alloxan and 4-Amino-3-(4-diethylamino-1-methylbutylamino)anisole. By A. MCCOUBREY and W. WEBSTER.

VARIOUS 9-basically substituted *iso*alloxazines have been described recently (Hall and Turner, *J.*, 1945, 699; King and Acheson, *J.*, 1946, 681; Neeman, *ibid.*, p. 811; Adams, Weisel, and Mosher, *J. Amer. Chem. Soc.*, 1946, **68**, 883), and in view of this the following observation appears to be worthy of note.

During attempts to synthesise 7-methoxy-9-(4-diethylamino-1-methylbutyl)*iso*alloxazine (I) a product was isolated which appears to be a compound between alloxan and (I).



(I.)



(II.)

Condensation of alloxan and 4-amino-3-(4-diethylamino-1-methylbutylamino)anisole in cold acetic–boric acid solution in the dark resulted in the rapid development of a yellow colour with a pronounced green fluorescence. A yellow microcrystalline compound was isolated, the analysis of which indicated that it was a product formed from (I) and alloxan. While this work was in progress Kipnis, Weiner, and Spoerri (*J. Amer. Chem. Soc.*, 1947, **69**, 799) described the isolation of (I) which was obtained when condensation was effected in boiling acetic–boric acid solution. This work has now been repeated and confirmed, and the products have been compared and shown to differ in properties. The complex was stable to cold aqueous alkali and could not be extracted from alkaline solution by chloroform.

The condensation of alloxan with aromatic amines (Pellizarri, *Gazzetta*, 1887, **17**, 412) and with phenols (D.R.-P. 107,720, 115,817; Schwyzer, *Chem. Zentr.*, 1930, **54**, 839) to form aldol-type products furnishes a clue to the possible structure of the complex, and it is tentatively suggested that the product has the structure (II). It is noteworthy that the majority of the 9-basically substituted *iso*alloxazines described in the literature have been substituted in the 6-position—a possible reason why products similar to that now described have not been encountered in the *iso*alloxazine series.

Condensation of alloxan and 4-amino-3-(4-diethylamino-1-methylbutylamino)anisole in aqueous hydrochloric acid gave 7-methoxyalloxazine by cleavage of the side chain (cf. Hall and Turner, *loc. cit.*), and a similar substance was produced by condensation of 3 : 4-diaminoanisole with alloxan, though the possibility of formation of 6-methoxyalloxazine in this case is not precluded.

4-Nitro-3-(4-diethylamino-1-methylbutylamino)anisole.—3 : 4-Dinitroanisole (Kipnis, Weiner, and Spoerri, *J. Amer. Chem. Soc.*, 1944, **66**, 1446) (16 g.) and 4-diethylamino-1-methylbutylamine (15·8 g.) were heated in cymene (350 c.c.) under reflux until a vigorous reaction began. Heating was discontinued until the reaction moderated, and was then resumed until no more nitrous fumes were evolved. The mixture was cooled, and extracted with hydrochloric acid (15%; 3 portions of 100 c.c.), and the acid extract washed once with ether, then basified. The precipitated oil was taken up in chloroform, dried (K_2CO_3), and filtered. Removal of the solvent left a dark red oil (19 g.) which distilled at 175—180°/0·4 mm. The *picrate* crystallised from alcohol in yellow prisms, m. p. 111—112° (Found : N, 15·5. $C_{16}H_{27}O_3N_3,C_6H_3O_7N_3$ requires N, 15·6%).

Condensation of Alloxan and 4-Amino-3-(4-diethylamino-1-methylbutylamino)anisole.—4-Nitro-3-(4-diethylamino-1-methylbutylamino)anisole (19·3 g.) was reduced catalytically in alcohol (100 c.c.) at 20° and 5 atmospheres pressure using platinum oxide (5%); 95% of the theoretical amount of hydrogen was absorbed during 1·75 hours. The solvent was removed from the filtered solution; the residue distilled at 154—165°/0·03 mm. Yield, 16·3 g.

The diamine (8·7 g.) dissolved in glacial acetic acid (130 c.c.) was added to a solution of alloxan (8·7 g.) and boric acid (17 g.) in the same solvent (900 c.c.), and the mixture was left at room temperature overnight. The yellow solution, which had a pronounced green fluorescence, was evaporated under reduced pressure, and the sticky residue washed repeatedly with ethyl acetate and then dried over potassium hydroxide in a vacuum. The residue (17 g.) separated from methanol–ethyl acetate as an orange microcrystalline powder (12·5 g.) which by repeated crystallisation became insoluble in methanol and was finally purified by solution in a minimal amount of water and addition of warm methanol. Orange micro-crystals slowly separated which decomposed without melting at 240°, and were readily soluble in water, giving a yellow solution with a strong green fluorescence [Found : C, 49·6; H, 6·0; N, 16·9; OMe, 5·7; H_2O (Karl Fischer), 11·1. $C_{24}H_{29}O_7N_7,3H_2O$ requires C, 49·5; H, 6·0; N, 16·9; OMe, 5·3; H_2O, 9·3%) (Material dried at 100°/0·1 mm. rapidly gained 11·3% in weight. Absorption of $3H_2O$ requires 10·3%).

3 : 4-Diaminoanisole.—3-Nitro-4-aminoanisole (15 g.) was added in small quantities during 0·5 hour to a hot solution of stannous chloride (80 g.) in hydrochloric acid (*d* 1·16; 140 c.c.) which was then heated on the steam-bath for 1 hour. The solution was cooled, basified, and extracted with ether, the extract dried (K_2CO_3), and the solvent removed; the residue distilled at 200—210°/21 mm. The distillate solidified and was crystallised from benzene (some decomp.), yielding reddish crystals (7·6 g.), m. p. 52°. The diamine dihydrochloride (1 g.) and benzil (1 g.) were heated on the steam-bath in aqueous alcohol

(50%; 5 c.c.) for one hour. 6-*Methoxy*-2 : 3-*diphenylquinoxaline* separated from the hot solution; it crystallised from alcohol in yellow prisms, m. p. 156° (Found : N, 8·8. $C_{21}H_{16}ON_2$ requires N, 9·0%).

6-(*or* 7)-*Methoxyalloxazine*.—3 : 4-Diaminoanisole dihydrochloride (6·2 g.) in water (15 c.c.) was added to a solution of alloxan (5·4 g.) in water (15 c.c.). A copious brown precipitate (6·75 g.) rapidly appeared and was filtered off after 6 hours at room temperature. This *product* separated from hot glacial acetic acid (600 c.c.) with solvent of crystallisation which could not be removed in a vacuum at 110°; it was, therefore, recrystallised from pyridine, and formed yellow microcrystals, which fell to a fine powder at 110° in a vacuum and did not melt below 300° (Found : N, 22·6; OMe, 12·8. $C_{11}H_8O_3N_4$ requires N, 23·0; OMe, 12·7%). A similar compound was produced in the condensation of alloxan with (II) in aqueous hydrochloric acid.

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