484. *The Conversion of Arylureas into Symmetrical Diarylureas. The Melting Points of Certain Substituted Ureas.*

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The preparation of 1-*ureido*-2- and 1-*ureido*-4-*alkoxynaphthalenes* is described and their conversion into the corresponding symmetrical *bisalkoxynaphthylureas* examined. The conversion into the *s*-diarylureas occurs particularly rapidly in the *para*-substituted series and accounts for the occurrence of indefinite melting points in certain substituted arylureas. The analogous behaviour of 2- and 4-diphenylylureas is also recorded.

THE conversion of arylureas above their melting points into symmetrical diarylureas has often been observed (*e.g.*, Sell, *Annalen*, 1863, **126**, 157). Davis *et al.* (*J. Amer. Chem. Soc.*, 1922, **44**, 2595; 1923, **45**, 1816) showed that arylureas dissociated in two ways, forming on the one hand *iso*cyanic acid and an aromatic amine (equation 1), and on the other ammonia and aryl *iso*cyanate (equation 2); recombination of the aromatic dissociation products according to equation 5 accounted for the production of the symmetrical diarylureas. The thermal rearrangement of 1-aryl-3-alkylureas into symmetrical diarylureas was accounted for similarly (see equations 3—6).

$$\mathrm{Ar{\cdot}NH{\cdot}CO{\cdot}NH_2} \longrightarrow \mathrm{Ar{\cdot}NH_2 + HNCO} \quad . \; . \; . \; . \; . \quad (1)$$

$$\mathrm{Ar{\cdot}NH{\cdot}CO{\cdot}NH_2} \longrightarrow \mathrm{Ar{\cdot}NCO + NH_3} \quad . \; . \; . \; . \; . \quad (2)$$

$$\mathrm{Ar{\cdot}NH{\cdot}CO{\cdot}NHAlk} \longrightarrow \mathrm{Ar{\cdot}NH_2 + Alk{\cdot}NCO} \quad . \; . \; . \; . \quad (3)$$

$$\mathrm{Ar{\cdot}NH{\cdot}CO{\cdot}NHAlk} \longrightarrow \mathrm{Ar{\cdot}NCO + Alk{\cdot}NH_2} \quad . \; . \; . \; . \quad (4)$$

$$\mathrm{Ar{\cdot}NH_2 + Ar{\cdot}NCO} \longrightarrow \mathrm{Ar{\cdot}NH{\cdot}CO{\cdot}NHAr} \quad . \; . \; . \; . \; . \quad (5)$$

$$\mathrm{Alk{\cdot}NH_2 + Alk{\cdot}NCO} \longrightarrow \mathrm{Alk{\cdot}NH{\cdot}CO{\cdot}NHAlk} \quad . \; . \; . \; . \; . \quad (6)$$

1-*Ureido*-2- and 4-*ureido*-1-*naphthol* were prepared by existing methods from the corresponding aminonaphthols, and were converted into the *methyl* and *ethyl ethers*. Prolonged fusion of 1-amino-2-naphthol hydrochloride with urea gave *di*-2-*hydroxy*-1-*naphthylurea*, also produced by heating 1-ureido-2-naphthol at 250° for one hour. *Di*-2-*alkoxy*-1-*naphthylureas* were obtained by heating 1-ureido-2-alkoxynaphthalenes above their melting points, or by boiling their aqueous solutions for several hours, and were identical with specimens prepared by the alkylation of di-2-hydroxy-1-naphthylurea. The rearrangement of 1-ureido-4-alkoxynaphthalene to symmetrical *di*-4-*alkoxy*-1-*naphthylureas* at elevated temperatures occurred with particular ease: conversion took place almost instantaneously and was completed by brief heating near the melting point of the starting material.

The ureidoalkoxynaphthalenes described are closely related to the intensely sweet 4-ureidophenetole (" Dulcin "). 1-Ureido-4-methoxy- and 1-ureido-4-ethoxy-naphthalene were found to be tasteless or very faintly bitter probably owing to the change of a benzene for a naphthalene nucleus and to their very limited solubility in water at ordinary temperatures. These results agree with the observation, that introduction of even a single alkyl group into the " Dulcin " molecule (as, for example, in 4-ureido-3-methylphenetole) suppresses the sweet taste. 4-Ureido-1-naphthol, produced, after a bitter, burning sensation, a persistent sweet taste; similar, but very faint effects were observed with the *ortho*-isomer.

The behaviour of arylureas on fusion recalls the frequent discrepancies in the reported melting points of certain urea derivatives, particularly asymmetric aryl-, diaryl-, and arylalkylureas (cf. Beilstein's Handbuch, 1929, **12**, 801, 941, 1292). The decomposition temperature of 4-bromophenylurea, for example, has variously been given at points between 220° and 296° (see experimental). Wheeler (*J. Amer. Chem. Soc.*, 1929, **51**, 3653), although noticing a difference in the behaviour of this compound on slow and rapid heating, was unable to account for these observations. Van Gelderen (*Rec. Trav. chim.*, 1933, **52**, 976), describing the preparation of a series of substituted *p*-diphenylylureas of the type $Ph \cdot C_6H_4 \cdot NH \cdot CO \cdot NR'R''$, has pointed out that the melting points of the majority of compounds studied were not sharp, and ascribed this to the changes represented by equations (3—6). The observation that the decomposition ranges of these derivatives depended on the rate of heating, the nature of the melting-point apparatus used, etc., led to the conclusion that melting points cannot be used for the characterisation of substituted ureas.

The results obtained in the present investigation have shown that the thermal conversion of aryl- into the corresponding diaryl-ureas, proceeding according to equations (1), (2), and (5), takes place extremely rapidly, often below the melting point, with arylureas containing certain substituents, particularly in the position *para* to the ureido-group, and is responsible for the occurrence of indefinite melting points. Thus, for example, whilst 2-diphenylylurea melted sharply at 158—160°, 4-diphenylylurea, heated under the same conditions, sintered at 180—190° and re-melted at 295—300°. This behaviour was accounted for by experiments which showed that 4-diphenylylurea was completely converted into bis-4-diphenylylurea, m. p. 316°, by heating at 210° for 10 minutes. The corresponding conversion of the *ortho*-isomer into *bis-2-diphenylylurea*, however, was incomplete after 1 hour's heating; a sample of the melt withdrawn after 10 minutes' fusion showed a nitrogen content corresponding to a mixture of 84% of starting material, and 16% of bis-2-diphenylylurea. On prolonged heating, small quantities of *2-diphenylylbiuret* were obtained in this conversion, but not in the others. The formation of biurets is readily accounted for by the following extension of Davis's mechanism:

$$Ar \cdot NH \cdot CO \cdot NH_2 + HNCO \longrightarrow Ar \cdot NH \cdot CO \cdot NH \cdot CO \cdot NH_2 \quad . \quad . \quad . \quad . \quad . \quad (7)$$

In determining the melting points of substituted ureas which undergo the above rearrangement rapidly it seems desirable to carry out the measurements under such conditions that conversion into the symmetrical diarylurea is avoided as far as possible. Reproducible values have now been determined by the following simple procedure: after the approximate softening temperature or melting range of the urea had been found, the bath temperature of the apparatus was raised 10—20° above that point, and samples inserted into the slowly cooling bath, until a temperature was reached at which a specimen just failed to liquefy. Insertion of another specimen at a temperature one degree higher caused instantaneous fusion, and could be taken as the "melting point" of the urea derivative under examination. Under these conditions, practically no conversion into diarylurea occurs, and samples withdrawn immediately after fusion showed nitrogen contents corresponding to the original arylurea. If left in the melting-point apparatus, the fused arylurea normally resolidified after a few seconds and then showed a second melting point, that of the diarylurea. This procedure gives satisfactorily reproducible physical constants for urea derivatives whose properties preclude slow heating. Using this method it has been found that melting points recorded in the literature for arylureas are indeed often those of the corresponding diarylureas, or mixtures of both. Thus, for example, 4-diphenylylurea melts sharply at 197—198°, whilst the "decomposition temperature," 210°, reported by van Gelderen (*loc. cit.*), is that of a mixture with bis-4-diphenylylurea. Similar considerations apply to the constants recorded by Herrmann (*Annalen*, 1922, **429**, 163) for 1-ureido-4-ethoxynaphthalene ("sintering at 205—207°, decomposition at 264—265°"). The compounnd was found to melt at 221—222°; short heating above this melting point rapidly converted it into *di-4-ethoxy-1-naphthylurea*, m. p. 266—267°. The analogous behaviour of 4-bromophenylurea is also described.

EXPERIMENTAL.

All m.p.s are uncorrected. Analyses are by Drs. Weiler and Strauss. M.p.s of *p*-substituted arylureas were determined by the method described in the theoretical section.

1-Ureido-2-naphthol.—(a) *By the action of urea.* 1-Amino-2-naphthol hydrochloride (20 g., 1 mol.), dissolved in a mixture of water (150 ml.) and glacial acetic acid (2 ml.), was treated with urea (40 g., 6·5 mols.) and the whole heated under reflux with mechanical stirring for one hour. After cooling of the solution to room temperature, the product was filtered off and freed from coloured impurities by boiling briefly under reflux with ethanol (40 ml.). The residue in sodium hydroxide solution (500 ml.; 2% w/v), was treated with sodium dithionite (1 g.), and stirred with charcoal at 60° for ½ hour. After the removal of the carbon, the product was precipitated by passage of sulphur dioxide. A second reprecipitation, and cooling to 0°, gave *1-ureido-2-naphthol* (15—18 g.; 60—72%) in white micro-crystalline plates, m. p. 224—225° (decomp.) (Found: C, 65·4; H, 5·0; N, 13·6. $C_{11}H_{10}O_2N_2$ requires C, 65·35; H, 4·95; N, 13·85%).

(b) *By the action of sodium cyanate.* To a solution of 1-amino-2-naphthol hydrochloride (10 g., 1 mol.) in water (150 ml.) at 30°, sodium cyanate (10 g., 3 mols.; saturated aqueous solution) was added with stirring. The product separated immediately as a greyish-purple solid. After two reprecipitations with sulphur dioxide 1-ureido-2-naphthol, m. p. 224—225° (decomp.), was obtained as a white micro-crystalline powder (8—9 g.; 63—71%) (Found: N, 13·9%). 1-Ureido-2-naphthol is difficultly soluble in hot methanol, ethanol, and acetone, and almost insoluble in benzene and light petroleum. Crystallization from ethanol yields shiny needles, m. p. 225—226° (decomp.).

1-*Ureido*-2-*methoxynaphthalene*.—1-Ureido-2-naphthol (4 g., 1 mol.), dissolved in sodium hydroxide solution (100 ml.; 5% w/v) was treated at 50° with methyl sulphate (12 g., 5 mols.) in two portions. The reaction mixture, from which the crude product separated immediately, was kept at 100° for 30 minutes, and maintained alkaline by the addition of more sodium hydroxide solution. After being cooled to 0° and filtered, the product was crystallized from dilute ethanol (200 ml.; 80%) and gave 1-*ureido*-2-*methoxynaphthalene*, m. p. 236—238°, in colourless lustrous plates (3·5 g.; 75%), which recrystallized from a large volume of boiling water as needles (Found: C, 66·9; H, 5·5; N, 11·8. $C_{12}H_{12}O_2N_2$ requires C, 66·7; H, 5·6; N, 13·0%). Tasteless.

1-*Ureido*-2-*ethoxynaphthalene*.—This *product*, obtained by the procedure used for the methoxy-compound in 60% yield, formed shiny needles, m. p. 194—196° (Found: C, 67·5; H, 6·0; N, 12·2. $C_{13}H_{14}O_2N_2$ requires C, 67·85; H, 6·1; N, 12·2%). It was sparingly soluble in water, producing a faint bitter taste.

1-*Acetamido*-2-*naphthyl Acetate*.—1-Ureido-2-naphthol (6 g., 1 mol.), in pyridine (50 ml.), was heated with acetic anhydride (30 g., 10 mols.) at 100° for two hours. The resulting liquid was poured into water (250 ml.), and well-developed prisms separated overnight (4·5 g.; 60%). After two crystallizations from ethanol (150 ml., 120 ml.) 1-acetamido-2-naphthyl acetate, m. p. 204—206°, was obtained in lustrous colourless prisms (Found: C, 68·7; H, 5·4; N, 5·5, 5·9. Calc. for $C_{14}H_{13}O_3N$: C, 69·1; H, 5·35; N, 5·8%). The m. p. was not depressed on admixture with authentic material (Michel and Grandmougin, *Ber.*, 1892, **25**, 3432). Alkaline hydrolysis gave lustrous plates of 1-acetamido-2-naphthol, m. p. 235—236° (decomp.).

Di-2-*hydroxy*-1-*naphthylurea*.—(a) *From* 1-*amino*-2-*naphthol hydrochloride*. An intimate mixture of 1-amino-2-naphthol hydrochloride (20 g., 1 mol.) and urea (24 g., 4 mols.) was fused at 160° in nitrogen. The temperature of the orange melt was raised slowly and maintained at 200° for 1 hour, while strong evolution of ammonia took place. The solidified product was broken up, and its alkaline solution (4% w/v sodium hydroxide solution) treated at 40° with charcoal, followed by precipitation with sulphur dioxide. After two reprecipitations *di*-2-*hydroxy*-1-*naphthylurea*, m. p. 214—216°, was obtained as a white micro-crystalline powder (14—15 g.; 81—87%) (Found: C, 73·0; H, 4·4; N, 7·9. $C_{21}H_{16}O_3N_2$ requires C, 73·3; H, 4·65; N, 8·1%).

(b) *From* 1-*ureido*-2-*naphthol*. 1-Ureido-2-naphthol (1 g.) was melted and maintained at 240° for 1 hour. Isolation of the product as described above gave di-2-hydroxy-1-naphthylurea (0·75 g.), m. p. 214—215° (Found: N, 8·7%).

Di-2-*methoxy*-1-*naphthylurea*.—(a) *From di*-2-*hydroxy*-1-*naphthylurea*. Treatment of the symmetrical hydroxy-compound with methyl sulphate as previously described (but under somewhat more drastic conditions—80°; 30 minutes' shaking) and two crystallizations from aqueous acetic acid, gave micro-crystalline needles of *di*-2-*methoxy*-1-*naphthylurea*, m. p. 268—270° (decomp), in excellent yield (Found: C, 73·8; H, 5·5; N, 7·25. $C_{23}H_{20}O_3N_2$ requires C, 74·2; H, 5·4; N, 7·5%).

(b) *From* 1-*ureido*-2-*methoxynaphthalene*. 1-Ureido-2-methoxynaphthalene (1 g.) was heated under reflux for 2 hours with water (250 ml.), in which it dissolved very gradually. The solution was slowly evaporated to small bulk (50 ml.) during 2 hours and cooled to 0°, and then deposited a product which gave di-2-methoxy-1-naphthylurea (0·5 g.), m. p. 268—270° (decomp.), from aqueous acetic acid. There was no depression of m. p. in admixture with material obtained by method (a) (Found: N, 7·35%).

(c) 1-Ureido-2-methoxynaphthalene (1 g.) was heated above its melting point in nitrogen for 30 minutes; ammonia was evolved and partial re-solidification occurred. Crystallization of the residue from aqueous acetic acid, with the addition of decolorizing carbon, gave di-2-methoxy-1-naphthylurea (0·4 g.), m. p. 268—270° (decomp.) not depressed on admixture with material obtained by method (a) (Found: N, 7·9%).

Di-2-*ethoxy*-1-*naphthylurea* was prepared by methods (a) and (c), and formed colourless needles, m. p. 246—247° (Found: N, 7·3, 7·5. $C_{25}H_{24}O_3N_2$ requires N, 7·0%).

4-*Ureido*-1-*naphthol*.—1-Amino-4-naphthol hydrochloride (10 g., 1 mol.) in water (100 ml.) was added dropwise within 15 minutes, with mechanical stirring, to a solution of sodium cyanate (10 g., 3 mols.) in water (120 ml.), cooled externally to 0°. The temperature of the reaction mixture was kept below 5° by the addition of ice. The pale purple solid obtained was dissolved in sodium hydroxide solution (200 ml.; 2% w/v), treated with charcoal at 50° for 30 minutes, and reprecipitated by the slow addition of excess of dilute sulphuric acid to the filtrate, previously cooled to 0°. After two further reprecipitations, 4-*ureido*-1-*naphthol*, m. p. 184—185° (decomp.), was obtained as a white micro-crystalline powder (8—9 g.; 80—90%) (Found: C, 64·9; H, 4·8; N, 13·3. $C_{11}H_{10}O_2N_2$ requires C, 65·35; H, 4·95; N, 13·85%). It turns pale purple on storage, is readily soluble in methanol, ethanol, and acetone and can be crystallized from ethanol–light petroleum. An aqueous solution of this compound produced, after a bitter burning sensation, a persistent sweet taste. Attempts to prepare 4-ureido-1-naphthol by boiling a solution of 1-amino-4-naphthol hydrochloride with urea failed.

1-*Ureido*-4-*methoxynaphthalene*.—Methylation of 4-ureido-1-naphthol as previously described gave a *product* (72% yield) which crystallized from ethanol–water (2 : 1) as white micro-crystalline needles, m. p. 224—225° (Found: C, 65·95; H, 5·45; N, 12·9. $C_{12}H_{12}O_2N_2$ requires C, 66·7; H, 5·6; N, 13·0%). The compound was very sparingly soluble in water and produced a faint bitter taste.

1-*Ureido*-4-*ethoxynaphthalene*.—This was prepared analogously. It was twice crystallized from ethanol and formed a silky mass of white micro-crystalline needles, m. p. 221—222° (Found: C, 67·6; H, 5·6; N, 11·9. Calc. for $C_{13}H_{14}O_2N_2$: C, 67·85; H, 6·1; N, 12·2%). Herrmann (*loc. cit.*) reports sintering at 205—207°, followed by decomposition at 264—265°. The bitter taste reported by this author for the compound is very faint and appears to be confined to its alcoholic solution.

Di-4-*hydroxy*-1-*naphthylurea*.—A mixture of finely ground 1-amino-4-naphthol hydrochloride (12 g., 1 mol.) and urea (12 g., 3 mols.) was put into a paraffin bath at 250°, and the temperature rapidly raised to 270°. The vigorous reaction accompanied by evolution of ammonia slackened after 15 minutes and heating was discontinued. The powdered melt (21 g.) was dissolved in warm sodium hydroxide solution (250 ml.; 3% w/v) containing a little sodium dithionite, and purified with charcoal, and the product precipitated from the filtrate at 0° with dilute hydrochloric acid. Two further reprecipitations gave *di*-4-*hydroxy*-1-*naphthylurea* as a pale-grey powder, m. p. 208—210° (decomp.) (Found: N, 8·6. $C_{21}H_{16}O_3N_2$ requires N, 8·1%). Fusion of the corresponding unsymmetrical urea derivative above the m. p. was unsuitable for the preparation of this compound.

Di-4-*methoxy*-1-*naphthylurea.*—1-Ureido-4-methoxynaphthalene (1 g.), was heated to 240° for 10 minutes. After rapid fusion, the material resolidified immediately and formed a white mass (0·9 g.; m. p. 306—307°), a small specimen of which was crystallized from ethanol and gave white micro-crystalline *di*-4-*methoxy*-1-*naphthylurea*, m. p. 310—312° (decomp.) (Found: N, 7·6. $C_{23}H_{20}O_3N_2$ requires N, 7·5%).

Di-4-*ethoxy*-1-*naphthylurea.*—This was prepared similarly and formed a micro-crystalline mass, m. p. 276—278° (decomp.) (Found: N, 7·4. $C_{25}H_{24}O_3N_2$ requires N, 7·0%).

Bis-2-*diphenylylurea.*—2-Diphenylylurea (1 g.) (Morgan and Walls, *J.*, 1932, 2225) was heated to about 200° for 1½ hours. The brown melt began to solidify after ½ hour and had set completely at the end of 1 hour. The powdered material was boiled with three successive portions of ethanol (3 × 20 ml.), giving an insoluble powdery residue of 2-*diphenylylbiuret*, m. p. 258—260° (0·2—0·3 g.) (Found: C, 65·6; H, 5·1; N, 16·3, 16·4. $C_{14}H_{13}O_2N_3$ requires C, 65·9; H, 5·1; N, 16·5%). The pale violet filtrates were decolorized with carbon and concentrated to small volume and then deposited clusters of lustrous needles (0·4—0·5 g.) of *bis*-2-*diphenylylurea*, m. p. 185—186° (Found: N, 7·95. $C_{25}H_{20}ON_2$ requires N, 7·7%).

In separate experiments, 2-diphenylylurea was fused at 200° for 5 and 10 minutes. The melts, which were completely soluble in ethanol (indicating absence of 2-diphenylylbiuret) were finely powdered, and extracted with a little cold water to remove traces of urea. The specimens showed nitrogen contents (12·6 and 12·3%) corresponding to the presence of 90 and 84% of the original unsymmetrical urea, respectively.

Bis-4-*diphenylylurea.*—4-Diphenylylurea (2·12 g.) (van Gelderen, *loc. cit.*) was maintained at 200—210° for 10 minutes. After 5 minutes, the substance softened and melted partially, but solidified on continued stirring. The cooled material was finely powdered, boiled with ethanol (30 ml.), filtered, and dried (1·6 g.; 87%). Crystallization of a specimen from a large volume of ethanol gave white micro-crystalline bis-4-diphenylylurea, m. p. 316—318° (Found: C, 82·3; H, 5·7; N, 7·65. Calc. for $C_{25}H_{20}ON_2$: C, 82·4; H, 5·5; N, 7·7%).

Di-4-*bromophenylurea.*—The m. p. of 4-bromophenylurea [reported as approximately 260° (decomp.) (Pinnow, *Ber.*, 1891, **24**, 4172), above 270° (decomp.) (Dains and Wertheim, *J. Amer. Chem. Soc.*, 1920, **42**, 2303), above 265° (decomp.) (Scott and Cohen, *J.*, 1922, **121**, 2034), at 220° or 296° (decomp.) (Wheeler, *J. Amer. Chem. Soc.*, 1929, **51**, 3653), and at 278° (Desai *et al.*, *J.*, 1934, 1186)] was found consistently to be 225—227° when determined by the technique described in this paper. 4-Bromophenylurea (1·5 g.) was heated to 240° for 8 minutes, and the white, amorphous, partially sublimed mass crystallized from glacial acetic acid (250 ml.), yielding lustrous needles of di-4-bromophenylurea, m. p. 314—316° (decomp.) (Found: N, 7·75. Calc. for $C_{13}H_{10}ON_2Br_2$: N, 7·6%). [The following m. p.s have been recorded for this compound: 320—330° (decomp.) (Biltz, *Annalen*, 1909, **368**, 227), 218—219° (Sah *et al.*, *J. Chinese Chem. Soc.*, 1936, **4**, 193), and 275—277° (Zetzsche *et al.*, *Ber.*, 1938, **71**, 1088).]

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