# The Reaction of Benzoyldicyandiamide [PhCO·NH·C(NH$_2$):N·CN] with Hydroxylamine Hydrochloride, to give Oxadiazoles

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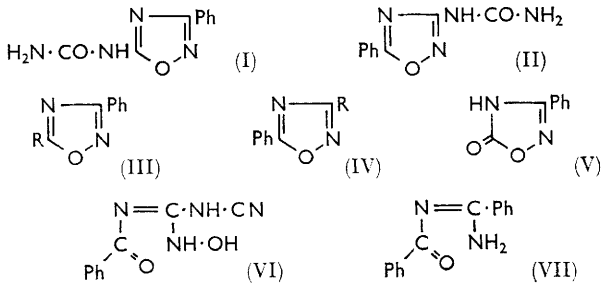
When benzoyldicyandiamide is treated with hydroxylamine hydrochloride, the product is a mixture of 3-phenyl-5-ureido-1,2,4-oxadiazole (I) (major component) and 5-phenyl-3-ureido-1,2,4-oxadiazole (II). The infrared spectrum of the urea (I) is discussed. The urea (II) is degraded by alkali to 3-amino-5-phenyl-1,2,4-oxadiazole; further degradation gives benzoic acid. 5-Phenyl-3-ureido-1,2,4-oxadiazole has been prepared in good yield by the Curtius reaction from 3-ethoxycarbonyl-5-phenyl-1,2,4-oxadiazole.



Kaiser [1] reported in 1946 that treatment of benzoyldicyandiamide [PhCO·NH·C(NH$_2$):N·CN] with hydroxylamine hydrochloride in boiling water gave 3-phenyl-5-ureido-1,2,4-oxadiazole (I) in >90% yield. The structure of the product was indicated by alkaline hydrolysis, which gave 3-phenyl-1,2,4-oxadiazol-5-one (V) (85%). However, in 1953 Adams, Kaiser, and Peters [2] assigned to the same product the structure of 5-phenyl-3-ureido-1,2,4-oxadiazole (II). The revision of structure also was based on alkaline degradation, which gave not only the oxadiazolone (V), as reported earlier, but also (12·5%) 3-amino-5-phenyl-1,2,4-oxadiazole (IV; R = NH$_2$). Isolation of the oxadiazolone (V) indicates that the urea was probably (I), for 5-amino-3-phenyl-1,2,4-oxadiazole (III; R = NH$_2$), an expected intermediate in the degradation of the urea (I), is readily hydrolysed [3] to the oxadiazolone (V). Adams, Kaiser, and Peters, however, reported that their 3-amino-5-phenyl-1,2,4-oxadiazole gave, on further hydrolysis, the oxadiazolone (V), although they isolated it in only 10% yield. They therefore attributed the production of the oxadiazolone from the urea to further degradation of the amine (IV; R = NH$_2$) by an unexplained mechanism.

Palazzo and Strani [4a] in 1960 prepared 5-azidocarbonyl-3-phenyl-1,2,4-oxadiazole (III; R = CON$_3$) by an unambiguous route and converted it by the Curtius reaction into 5-amino-3-phenyl-1,2,4-oxadiazole. In 1961 they similarly [4b] prepared 3-phenyl-5-ureido-1,2,4-oxadiazole and reported that it was indistinguishable from Kaiser's urea in melting point, infrared spectrum, and behaviour on hydrolysis.

The reaction of benzoyldicyandiamide with hydroxylamine hydrochloride has now been studied by us with the aid of reference compounds whose structure is certain. When the total crude urea obtained from benzoyldicyandiamide and hydroxylamine hydrochloride [1,2] was boiled with 2N-sodium hydroxide, the oxadiazolone (V) was obtained (70%), together with an alkali-insoluble product, m. p. 167—169° (6·5%). Hydrolysis of the recrystallised product gave similar results. However, when the urea (I) prepared by Palazzo and Strani's method was similarly degraded, only the oxadiazolone was isolated. Thin-layer chromatography and infrared analysis of the product with m. p. 167—169° showed that it was a mixture of 3-amino-5-phenyl-1,2,4-oxadiazole (IV; R = NH$_2$) (*ca.* 80%) and the isomer (III; R = NH$_2$) (*ca.* 20%). The melting point of the amine (IV; R = NH$_2$) (168—169°) was depressed only to 167—169° by admixture of 20% of the amine (IV; R = NH$_2$). The only product that could be isolated after alkaline degradation of the amine (IV; R = NH$_2$) was benzoic acid.




Careful thin-layer chromatography and infrared analysis (see Experimental section) of the crude product showed that it consisted of the urea (I) (>80%) and the urea (II) (*ca.* 20%). The proportion of the latter compound was reduced, probably to <10%, by one recrystallisation from ethanol (there is no evidence of it in Palazzo and Strani's published spectrum of Kaiser's urea). The melting point of the urea (I) depends on the rate of heating; it is lowered by <2° when 10% of the urea (II) is added.

Although Kaiser's urea is mainly (I), the mixture of amines derived from it consists mainly of (IV; R = NH$_2$). This is because that amine, unlike its isomer (III; R = NH$_2$), is relatively resistant to further degradation.

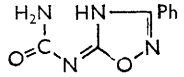
Adams, Kaiser, and Peters [2] suggested a possible mechanism, based on a cyclic form of benzoyldicyandiamide, for the production of the urea (II). Alternatively, the amino group of benzoyldicyandiamide could be attacked by hydroxylamine, to give the intermediate (VI). The latter would probably [5] cyclise readily to an oxadiazole; addition of water to the –NH·CN side-chain would then give the urea (II). A comparable replacement of the amino group of the acylated benzamidine (VII) by –NH·OH has been postulated [5] to

[1] D. Kaiser, U.S.P. 2,399,599 (*Chem. Abs.*, 1946, **40**, 4228).
[2] P. Adams, D. Kaiser, and G. Peters, *J. Org. Chem.*, 1953, **18**, 934.
[3] G. Ponzio, *Gazzetta*, 1932, **62**, 854.
[4] G. Palazzo and G. Strani, (*a*) *Gazzetta*, 1960, **90**, 1290; (*b*) *Ann. Chim.* (*Italy*), 1961, **51**, 130.
[5] F. Eloy, R. Lenaers, and R. Buyle, *Bull. Soc. chim. belges*, 1964, **73**, 518.

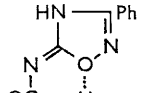
account for the formation [6] of 3,5-diphenyl-1,2,4-oxadiazole from (VII) and hydroxylamine.

The infrared spectrum in Nujol of Kaiser's unrecrystallised urea has a strong band at 1725 cm.$^{-1}$ and a much weaker band at 1770. In dimethyl sulphoxide solution there is a strong band at 1720, but none near 1770. However, when Kaiser's urea is recrystallised from ethanol, the band at 1725 disappears from the Nujol spectrum and that at 1770 is much intensified. The same behaviour is observed when the crude urea (I) prepared by Palazzo and Strani's method [4a] is recrystallised. The band at 1725 cm.$^{-1}$ is due to an unstrained carbonyl group, possibly as in (Ia). The shift to 1770 on recrystallisation is due to strain, presumably induced by an increased H···O bond length [7] in a hydrogen-bonded form, *e.g.*, (Ib), or, as suggested by Palazzzo and Strani,[4a] (Ic).

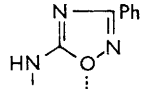
The urea (I) and the amine (III; R = $NH_2$) were prepared by Palazzo and Strani's method; a variation of their synthesis gave the urea (II) and the known [1,5,8,9] amine (IV; R = $NH_2$).



(Ia)



(Ib)



(Ic)

The ester (IV; R = $CO_2Et$) was prepared from ethoxycarbonylformamidoxime and benzoyl chloride.[9] The amidoxime was obtained from ethyl cyanoformate by treatment with hydrogen sulphide and reaction of the resultant thioamide with hydroxylamine (direct treatment of ethyl cyanoformate with hydroxylamine gave inferior results). The acid azide (IV; R = $CON_3$) was prepared from the ester (IV; R = $CO_2Et$) through the hydrazide; when heated in toluene it gave the isocyanate (IV; R = NCO), which was not isolated; this reacted with ammonia to give the urea (II), and with ethanol to give the urethane (IV; R = NH·$CO_2Et$). Alkaline hydrolysis of the urethane gave the amine (IV; R = $NH_2$). The urethane (IV; R = NH·$CO_2Et$) was recovered unchanged from boiling 2N-hydrochloric acid and from cold 36N-sulphuric acid.

## EXPERIMENTAL

Ultraviolet spectra were measured in ethanol. The internal reference standard for proton magnetic resonance spectra was tetramethylsilane. Thin-layer chromatography was carried out on plates coated with Kieselgel G containing 0·2% of uranyl acetate; spots were detected in ultraviolet light. Melting points are corrected.

*5-Amino-3-phenyl-1,2,4-oxadiazole* (III; R = $NH_2$).—This amine, prepared by Palazzo and Strani's method,[4a] had m. p. 154—155° (from water) (lit.,[4a] 153—154°), $\lambda_{max.}$ 225 mμ (ε 16,800), $\nu_{max.}$ ($CHBr_3$) 3480, 3380 ($NH_2$), 1642s (C=N), τ ($CDCl_3$) 2·10 ($NH_2$), 1·98—2·55 ($C_6H_5$) (Found: C, 59·8; H, 4·5; N, 25·9. Calc. for $C_8H_7N_3O$: C, 59·6; H, 4·4; N, 26·1%).

*3-Phenyl-5-ureido-1,2,4-oxadiazole* (I).—This urea, prepared by Palazzo and Strani's method,[4b] had m. p. 237—238° (decomp.) (from ethanol) (lit.,[4b] 237—238°), $\lambda_{max.}$ 232 mμ (ε 25,900), $\nu_{max.}$ (Nujol) 3400, 3240 (NH and $NH_2$), 1770 cm.$^{-1}$ (CO), τ ($Me_2SO$) −1·24 (NH), 2·59 ($NH_2$), 1·73—2·50 ($C_6H_5$) (Found: C, 52·6; H, 3·85; N, 27·2. Calc. for $C_9H_8N_4O_2$: C, 52·9; H, 3·95; N, 27·4%).

*Ethoxycarbonylformamidoxime* (with Dr. B. W. Nash).—A solution of sodium (104·8 g.) in ethanol (2 l.) was added to stirred hydroxylamine hydrochloride (312·7 g.) in warm ethanol (3·3 l.). The sodium chloride was filtered off, ethyl thiocarbamoylformate [10] (399 g.) added to the stirred filtrate, and the mixture stirred until homogeneous and left overnight. Most of the solvent was removed; the solution, on cooling, deposited ethoxycarbonylformamidoxime (368 g., 93%), m. p. 100—102° (lit.,[11] 99·5—100°).

*3-Azidocarbonyl-5-phenyl-1,2,4-oxadiazole* (IV; R = $CON_3$).—3-Hydrazidocarbonyl-5-phenyl-1,2,4-oxadiazole [9] was converted by conventional methods [4a] into the azide (68%), m. p. 85—87° (decomp.) (lit.,[9] 85—87°), $\lambda_{max.}$ 252 mμ (ε 22,300), $\nu_{max.}$ ($CHBr_3$) 2175, 2140 ($N_3$), 1702 cm.$^{-1}$ (CO) (Found: C, 50·6; H, 2·3; N, 32·55. Calc. for $C_9H_5N_5O_2$: C, 50·2; H, 2·3; N, 32·55%).

*5-Phenyl-3-ureido-1,2,4-oxadiazole* (II).—3-Azidocarbonyl-5-phenyl-1,2,4-oxadiazole (700 mg.) in dry toluene (7 ml.) was heated slowly to 85° and, after 10 min., refluxed gently for 10 min. The cooled solution was saturated with dry ammonia and filtered after 6 hr. The solid was washed with toluene, leaving the *product* (530 mg., 80%), m. p. 228—229° (decomp.) (from ethanol), $\lambda_{max.}$ 239 mμ (ε 18,000), $\nu_{max.}$ (Nujol) 3460 (NH), 1708 (CO), 748, 695 cm.$^{-1}$ (Ph), τ ($Me_2SO$) 0·05 (NH), 1·77—2·50 ($C_6H_5$), 3·23 ($NH_2$) (Found: C, 53·1; H, 3·95; N, 27·6. $C_9H_8N_4O_2$ requires C, 52·9; H, 3·95; N, 27·4%).

*3-Ethoxycarbonyl 5-Phenyl-1,2,4-oxadiazole* (IV; R = NH·$CO_2Et$).—3-Azidocarbonyl-5-phenyl-1,2,4-oxadiazole (3·60 g.) was converted into the isocyanate as just described, and the toluene removed under reduced pressure. The residue was refluxed in dry ethanol (35 ml.) for 30 min., the ethanol evaporated, and the residue recrystallised from light petroleum (b. p. 100—120°). The *product* separated as long needles (2·85 g., 73%), m. p. 115·5—117·5°, $\lambda_{max.}$ 237 mμ (ε 22,400), $\nu_{max.}$ ($CHBr_3$) 3400 (NH), 1758, 1200 cm.$^{-1}$ ($CO_2Et$) (Found: C, 56·3; H, 4·8; N, 17·8. $C_{11}H_{11}N_3O_3$ requires C, 56·65; H, 4·75; N, 18·0%).

*3-Amino-5-phenyl-1,2,4-oxadiazole* (IV; R = $NH_2$).—The urethane (IV; R = NH·$CO_2Et$) (1·47 g.) was refluxed in 2N-sodium carbonate (450 ml.) for 1·5 hr. The solution was cooled slowly, and deposited long needles of 3-amino-5-phenyl-1,2,4-oxadiazole (900 mg., 90%), m. p. 168—169° (lit.,[5,9] 168—169°), $\lambda_{max.}$ 238—240 mμ (ε 16,100), $\nu_{max.}$ ($CHBr_3$) 3470, 3380 ($NH_2$), 1610s (C=N), 745 cm.$^{-1}$ (Ph), τ ($CDCl_3$) 1·70—2·50 ($C_6H_5$), 3·67 ($NH_2$) (Found: C, 59·5; H, 4·7; N, 26·3. Calc. for $C_8H_7N_3O$: C, 59·6; H, 4·4; N, 26·1%).

*Reaction of Benzoyldicyandiamide with Hydroxylamine Hydrochloride.*—Benzoyldicyandiamide [12] (6·58 g.) was suspended in water (75 ml.) and stirred, and hydroxylamine

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[7] N. Sidgwick, "The Chemical Elements and their Compounds," Clarendon Press, Oxford, 1950, p. 30.
[8] H. Wieland and H. Bauer, *Ber.*, 1907, **40**, 1680.
[9] G. Strani and A. Garau, *Gazzetta*, 1963, **93**, 482.
[10] W. R. Boon, *J. Chem. Soc.*, 1945, 602.
[11] G. Ulpiani, *Gazzetta*, 1912, **42**, 259.
[12] P. Adams, D. Kaiser, D. Nagy, G. Peters, R. Sperry, and J. Thurston, *J. Org. Chem.*, 1952, **17**, 1162.

hydrochloride (2·59 g.) in water (75 ml.) added. The mixture was refluxed for 5 min., then boiling water (50 ml.) was added and refluxing continued for 30 min. The mixture of ureas (I) and (II) (6·66 g., 92·5%) had m. p. 228—230° (decomp.) (Found: C, 53·5; H, 4·4; N, 27·1. Calc. for $C_9H_8N_4O_2$: C, 52·9; H, 3·95; N, 27·4%). Recrystallisation from ethanol gave m. p. 236—238° (decomp.) (Found: C, 52·7; H, 4·2; N, 27·2%). Thin-layer chromatography was carried out in benzene–ethyl acetate (9 : 1). Reference spots of (I) and (II) were applied, and the plate run for 20 min. then dried and re-run in 50% benzene–ethyl acetate. The mixture was separated into two components, of $R_F$ 0·13 and 0·28, corresponding to (II) and (I), respectively. The ratio (I) : (II), estimated from $\nu_{max.}$ (Nujol) at 1725 and/or 1770 cm.$^{-1}$ for (I) and 1708 cm.$^{-1}$ for (II), was *ca.* 80 : 20 in the crude product and *ca.* 90 : 10 in the recrystallised product.

*Alkaline Hydrolysis of Kaiser's Urea.*—The crude product from the preceding experiment (4·10 g.) was refluxed for 2·5 hr. in water (25 ml.) containing sodium hydroxide (2·01 g.). The yellow solution was concentrated to 20 ml., cooled slowly, and refrigerated overnight. The solid (210 mg., 6·5%) had m. p. 167—169°. Thin-layer chromatography (50% benzene–ethyl acetate) separated the mixture into two components (violet fluorescence) of the same $R_F$ values as (III; R = $NH_2$) (weaker) and (IV; R = $NH_2$) (stronger), respectively. Infrared analysis based on $\nu_{max.}$ at 1642 cm.$^{-1}$ [for (III; R = $NH_2$)] and 1610 cm.$^{-1}$ [for (IV; R = $NH_2$)] showed the ratio of (III; R = $NH_2$) to (IV; R = $NH_2$) to be *ca.* 20 : 80.

The filtrate was acidified to pH 5, and it deposited the crude oxadiazolone (V) (2·27 g., 70%), m. p. 190—192°. Solution in sodium hydroxide, filtration, and acidification gave (V), m. p. and mixed m. p. 197° (lit.,[13] m. p. 197°), identical (infrared spectrum) with an authentic sample. Hydrolysis of Kaiser's recrystallised urea gave a similar mixture of amines (6%) and, after acidification, compound (V) (68%).

*Alkaline Hydrolysis of* 3-*Phenyl*-5-*ureido*-1,2,4-*oxadiazole* (I).—The urea (I) (500 mg.), prepared from the isocyanate (III; R = NCO), was degraded as just described, but the amine (III; R = $NH_2$) could not be isolated after concentration, seeding, and refrigeration, and it could not be detected by thin-layer chromatography. When acidified the solution gave the oxadiazolone (V) (350 mg., 89%), m. p. 197°.

*Alkaline Hydrolysis of* 5-*Phenyl*-3-*ureido*-1,2,4-*oxadiazole* (II).—The urea (II) (300 mg.) in boiling ethanol (60 ml.) was refluxed with aqueous 2N-sodium hydroxide (20 ml.) for 2 hr.; ammonia was evolved. The yellow solution was refrigerated for 48 hr., but no solid separated. Ethanol was removed under reduced pressure, and the volume was made up to 30 ml. with water. The solid that separated (150 mg.) had m. p. 164—170°; it was a mixture of starting material (*ca.* 40%) and 3-amino-5-phenyl-1,2,4-oxadiazole (*ca.* 60%) (thin-layer chromatography and infrared analysis). Extraction of the mixture (120 mg.) with cold ethanol gave the amine (40 mg.); this contained a little of the urea (II).

*Alkaline Hydrolysis of* 3-*Amino*-5-*phenyl*-1,2,4-*oxadiazole*.—The amine (IV; R = $NH_2$) (161 mg.) was refluxed for 3 hr. in 2N-sodium hydroxide (10 ml.). The solution was cooled and filtered, and the filtrate acidified to pH 5, but no solid separated on refrigeration. The pH was then adjusted to 1 (2N-HCl), and the solution refrigerated for 10 days. Benzoic acid (27 mg., 22%) separated, m. p. and mixed m. p. 122°, and was identified by its infrared spectrum. The amine (IV; R = $NH_2$) was recovered almost quantitatively after being refluxed for 30 min. in aqueous 0·5N-sodium hydroxide.

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[13] E. Falck, *Ber.*, 1885, **18**, 2467.