Experimental Section

Analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Melting points are corrected. Chromatograms were developed by the ascending technique with Whatman No. 1 paper and were viewed under ultraviolet light primarily of wavelength 253.8 mμ. The solvent systems employed were (A) 3% ammonium chloride; (B) 5% disodium hydrogen phosphate–isoamyl alcohol (3:2); (C) isopropyl alcohol–water–28% ammonium hydroxide (7:2:1); and (D) *t*-butyl alcohol–methyl ethyl ketone–88% formic acid–water (40:30:15:15 v/v). The ultraviolet absorption data are given in Table I and chromatographic data in Table II. The p*K* values were determined by methods described,[12] at 20°, spectrophotometrically with 0.01 *M* buffers,[13] or potentiometrically with 0.01 *M* solutions. The infrared data were obtained using a Perkin-Elmer Model 221 spectrophotometer by the potassium bromide disk method.

TABLE II

Compd	R_f in solvents[a] A	B	C	D
1-Hydroxyhypoxanthine (IIa)	0.64	0.62	0.20	0.44
1-Hydroxyinosine (IIb)	0.82	0.80	0.30	0.30
Adenine 1-N-oxide	0.62	0.48[b]	0.50	0.49
2-Azaadenine 1-N-oxide	0.59	0.49[c]	0.53	0.36
Hypoxanthine	0.58	0.56	0.45	0.41
Adenosine 1-N-oxide	0.75	0.71[b]	0.38	0.38
Unknown by-product	0.15[d]	0.07[d]	0.11[d]	0.08[d]

[a] See Experimental Section for solvents. [b] Reference 6. [c] Reference 5. [d] Fluorescent.

1-Hydroxyhypoxanthine (IIa).—Adenine 1-N-oxide[11] (20.0 g, 0.13 mole) was suspended in a solution containing 36.8 g of $NaNO_2$ (0.52 mole) in 650 ml of water. The mixture was cooled in an ice bath to about 10°, and 140 ml of 50% aqueous acetic acid was added dropwise with stirring over a period of 30–40 min. The temperature of the solution did not rise above 10° during this period. After the addition of acid was complete, the solution was heated at 70–80° for 2 hr, then cooled to 10°. The precipitate was collected and washed with alcohol and ether to afford 13.7 g of a yellow powder. The crude product was dissolved in *ca.* 1 l. of hot dilute ammonia (pH 8–9) and the solution was allowed to cool and stand overnight. The fine yellow powder which precipitated (1.8 g) was collected and washed with ethanol and ether. The filtrate was concentrated under vacuum to about 500 ml, and an additional 2.2 g of yellow product was obtained. Both fractions were identical chromatographically and migrated as a single bright fluorescent spot. The pale yellow filtrate was then treated with charcoal (Darco), and the pH of the colorless solution was adjusted to 5.5 to 6 by addition of glacial acetic acid. The 1-hydroxyhypoxanthine slowly precipitated as a fine white microcrystalline solid, which proved to be chromatographically and analytically pure: yield 9.5 g (47%), mp 356° (decomposed with darkening above 340°).

Anal. Calcd for $C_5H_4N_4O_2$: C, 39.48; H, 2.65; N, 36.84. Found: C, 39.45; H, 2.73; N, 36.98.

A sample of analytically pure IIa, obtained from an aqueous solution and stored in a bottle for 4 months, was dried at 100° for 2 hr. The sample lost 0.06% of its weight. It was redried at 140° for 3 hr and lost an additional 0.04% of its weight. The sample gained no weight whatsoever when allowed to equilibrate with the atmosphere overnight. It is probable that the extreme hygroscopicity (average weight loss 10.1%) encountered by Taylor, Cheng, and Vogel[4] is due to hydration of impurities rather than hydration of IIa.

A solution of 75 mg of IIa dissolved in 10 ml of 0.1 *N* NaOH and containing *ca.* 400 mg of activated Raney nickel was hydrogenated at room temperature and 1 atm for 60 hr. An aliquot was chromatographed in solvent C and contained two spots, one corresponding to hypoxanthine and the other to unchanged IIa. A sample was chromatographed on a cellulose plate in solvent C and the two bands were quantitatively eluted with 0.1 *N* NaOH. Calculation of the molar quantities from the optical densities of the elution solutions indicated 10% of the N-oxide had been reduced to hypoxanthine under these conditions.

1-Hydroxyinosine (IIb).—Adenosine 1-N-oxide[11] (12.04 g, 0.04 mole) was suspended in a solution of 8.28 g (0.12 mole) of $NaNO_2$ dissolved in 80 ml of dimethylformamide. To the reaction mixture 20 ml of 50% aqueous acetic acid was added dropwise with stirring at room temperature over a period of 10–15 min. After the addition of acid was complete, the solution was stirred at room temperature for 1 hr and 50–60° for 2 hr. To this, when cooled, was added 600 ml of ether, which caused the separation of a yellow oil. The ether layer was discarded and the oily residue was washed with two 200-ml portions of ether. The yellow oil was dissolved in 400 ml of hot methanol and induced to crystallize by slow removal of the solvent on a steam bath until crystals began to form and then cooling the solution. A fine white precipitate was obtained which was collected and washed with ether to yield 4.50 g of a white microcrystalline powder. An additional 0.51 g was obtained from the mother liquors by successive reductions in volume and chilling.

The crude product (5.01 g) was dissolved in 15 ml of water and desalted by percolating the solution through a column containing Dowex 50, hydrogen form (W × 4, 20–50 mesh), and eluting with water. The elution was followed by monitoring the optical density of the eluate at 228 mμ.

The solvent was removed under reduced pressure while the temperature of the solution was maintained at 35–40°. The product, which crystallized from solution as large colorless prisms, was collected and washed with ethanol and ether to yield 2.40 g (21%) of analytically pure 1-hydroxyinosine, mp >400°, gradual decomposition and charring above 170°.

Anal. Calcd for $C_{10}H_{12}N_4O_6$: C, 42.14; H, 4.52; N, 19.65. Found: C, 42.24; H, 4.30; N, 19.80.

No hydrolysis of the sugar occurred during the ion-exchange elution (pH >4) nor did it take place in 0.1 *N* hydrochloric acid solution at room temperature. When a solution of 56 ml of IIb in 5 ml of *N* hydrochloric acid was warmed on a steam bath, complete hydrolysis was accomplished in 15 min. The product isolated from the reaction medium was shown to be chromatographically and spectrally identical with an authentic sample of IIa: yield 17.6 mg (58%).

Acknowledgment.—We wish to acknowledge the preliminary studies on this problem by Dr. Alfredo Giner-Sorolla and Dr. Ronald M. Cresswell. Dr. George Bosworth Brown wishes to thank Professor A. Albert and Dr. D. D. Perrin, The John Curtin School of Medical Research, Canberra, Australia, for hospitality and advice on the p*K* determinations.

(12) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," John Wiley and Sons, Inc., New York, N. Y., 1962.

(13) D. D. Perrin, *Australian J. Chem.*, **16**, 572 (1963).

The Preparation and Cyclization of Chloroethyl Carbazates. Some Clarifications[1]

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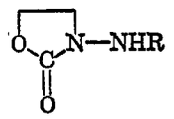
During the course of studies on 2-oxazolidinone chemistry, we were interested in preparing some 3-(substituted amino)-2-oxazolidinones (I). A possible route to these compounds involved the cyclization of (2-chloroethyl) 3-substituted carbazates (II). We have

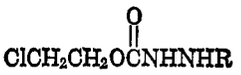
(1) This research was supported by the Advanced Research Projects Agency, Propellant Chemistry Office, under Contract NOrd 18728, and was monitored by the Bureau of Naval Weapons, RMMP, under Contract NOw 65-0277-c.

found that the literature in this area contains several inaccuracies in the designations of structures of compounds. This paper presents evidence on the actual structure of these materials.

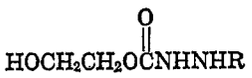
Delaby[2,3] treated ethylene carbonate with benzylhydrazine and methylhydrazine to obtain the hydroxyethyl esters IIIa and IIIb. Compounds IIIa and IIIb were converted to chloroethyl esters IIa and IIb, and IIa was cyclized to 3-benzylamino-2-oxazolidinone (Ia). No mention was made of an attempted cyclization of IIb.



Ia, R = $-CH_2C_6H_5$

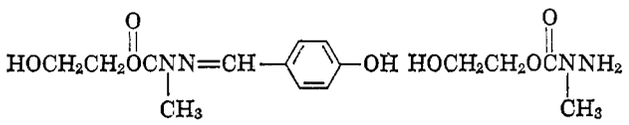


IIa, R = $-CH_2C_6H_5$
b, R = $-CH_3$



IIIa, R = $-CH_2C_6H_5$
b, R = $-CH_3$

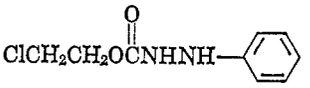
When the reaction of ethylene carbonate and methylhydrazine was repeated by Delaby's[3] procedure, a product was obtained whose physical properties were identical with those described by Delaby. However, the infrared spectrum of this material had a band at 1640 cm^{-1} strongly indicative of a free amino group. Reaction with *p*-hydroxybenzaldehyde gave the Schiff base IV and showed that the compound was actually the isomeric (2-hydroxyethyl) 2-methylcarbazate (V).[4]



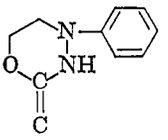
IV V

This evidence that methylhydrazine reacts with ethylene carbonate at the alkylated nitrogen suggested that on electronic grounds benzylhydrazine should react similarly to give a 2-substituted rather than a 3-substituted carbazate. However, the infrared spectrum of IIIa had no band which could be attributed to a free amino group. A synthetic proof of structure was derived from condensation of 3-amino-2-oxazolidinone with benzaldehyde to give 3-benzylideneamino-2-oxazolidinone[5] which was then catalytically reduced to 3-benzylamino-2-oxazolidinone (Ia). Compound Ia prepared by this route was identical with the compound obtained from IIIa by chlorination and cyclization. Possibly, with benzylhydrazine, a steric effect may be operative which outweighs the electronic effect.

Dox[6] prepared (2-chloroethyl) 3-phenylcarbazate (VI) by the direct reaction of phenylhydrazine and 2-chloroethyl chloroformate. Compound VI was then cyclized to a material postulated to be the oxadiazinone VII.

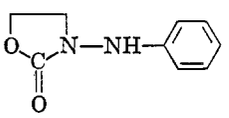


VI

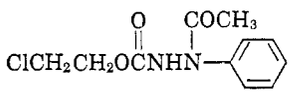


VII

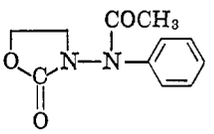
The structure of the phenylcarbazate VI was confirmed by the absence of a free amino band in the infrared,[7] but, on the basis of Delaby's[2] cyclization of the benzylcarbazate (IIa) to the oxazolidinone (Ia), it was felt that this cyclization product might be 3-anilino-2-oxazolidinone (VIII). Proof of structure VIII was obtained from the reaction of 2-chloroethyl chloroformate and 1-acetyl-1-phenylhydrazine[8] to give (2-chloroethyl) 3-acetyl-3-phenylcarbazate (IX), which was then cyclized to 3-(N-acetyl-N-phenylamino)-2-oxazolidinone (X). Acetylation of the material described as VII gave a compound identical with X and established that the cyclization product of carbazate VI was indeed the oxazolidinone (VIII).[9]



VIII



IX



X

Experimental Section[10]

Reaction of Ethylene Carbonate and Methylhydrazine. (2-Hydroxyethyl) 2-Methylcarbazate (V).—The procedure of Delaby[3] was followed to give a 58% yield of V, a colorless liquid: bp 139–141° (0.5 mm); $n^{20}D$ 1.475 [lit.[3] bp 140–142° (0.5 mm); $n^{20}D$ 1.474]; infrared (liquid smear), 3400, 3310, 3250, 2910, 1690, 1640, 1535, 1480, 1445, 1400, 1360, 1260, 1180, 1075, 910, and 770 cm^{-1}.

(2-Hydroxyethyl) 2-Methyl-3-(*p*-hydroxybenzylidene)carbazate (IV).—A solution of 1.34 g (0.01 mole) of V and 1.22 g (0.01 mole)

(2) R. Delaby, C. Warolin, and F. Brustlein, *Compt. Rend.*, **237**, 1714 (1954).

(3) R. Delaby, F. Brustlein, C. Warolin, and P. Chabrier, *Bull. Soc. Chim. France*, 2056 (1961).

(4) Addition of thionyl chloride to V, as described by Delaby,[3] gave a solid (mp 140–150°) formulated as the hydrochloride of IIb. Fractional recrystallization from 2-propanol resulted in identification of this material as a mixture of the hydrochloride of (2-chloroethyl) 2-methylcarbazate (mp 153–155°) and the hydrochloride of V (mp 116–118°).

(5) G. Gever, C. O'Keefe, G. Drake, F. Ebetino, J. Michels, and K. Hayes, *J. Am. Chem. Soc.*, **77**, 2277 (1955).

(6) A. W. Dox, *ibid.*, **48**, 1951 (1926).

(7) Delaby[3] prepared (2-hydroxyethyl) 3-phenylcarbazate by the reaction of phenylhydrazine and ethylene carbonate. It also had no free amine band in the infrared.

(8) R. Behrend and W. Reinsberg, *Ann.*, **377**, 208 (1910).

(9) Based on these observations, there exists a strong possibility that the compound described by Dox[6] as 4-phenyldihydro-1,3,4-oxadiazepin-2-one is actually 3-anilinodihydro-1,3-oxazin-2-one.

(10) Melting points were taken on a calibrated Fisher-Johns apparatus. Infrared spectra were taken on a Perkin-Elmer Model 137 Infracord spectrophotometer. Microanalyses were by Research Service Department, Central Research Division, American Cyanamid Co.

of *p*-hydroxybenzaldehyde in 25 ml of absolute alcohol was refluxed for 16 hr. The solution was concentrated to 15 ml and chilled. The precipitate was filtered, dried, and recrystallized from absolute alcohol to give 1.60 g (73%) of IV, a pale yellow, crystalline solid, mp 145–146°.

Anal. Calcd for $C_{11}H_{14}N_2O_4$: C, 55.45; H, 5.92; N, 11.76. Found: C, 55.65; H, 6.17; N, 11.98.

3-Benzylamino-2-oxazolidinone (Ia). A. Cyclization of (2-Chloroethyl) 3-Benzylcarbazate (IIa).—The procedure of Delaby[2] was followed to prepare (2-hydroxyethyl) 3-benzylcarbazate (IIIa) from benzylhydrazine and ethylene carbonate and to convert IIIa to IIa. Cyclization of IIa to Ia, which was not explicitly described in Delaby's papers, was performed as follows. A solution of 2.29 g (0.01 mole) of IIa in 25 ml of absolute alcohol stirred under nitrogen was treated, over 10 min, with 0.23 g (0.01 g-atom) of sodium in 10 ml of absolute alcohol. The solution was stirred 0.5 hr and then refluxed 1 hr. After cooling, the precipitated sodium chloride was filtered and the alcohol was stripped *in vacuo*. Recrystallization of the residue from benzene gave 1.06 g (55%) of Ia as small colorless needles, mp 70–72° (lit.[2] mp 70°).

B. Reduction of 3-Benzylideneamino-2-oxazolidinone.—3-Benzylideneamino-2-oxazolidinone was prepared in 95% yield (mp 143–145°) from 3-amino-2-oxazolidinone and benzaldehyde by the procedure of Gever, *et al.*[5] To 5.0 g (0.026 mole) of the benzylidene compound in 100 ml of absolute alcohol stirred under nitrogen was added 2 g of 5% palladium on charcoal. Hydrogen gas was bubbled through the solution for 4 hr. The catalyst was filtered and the solution was concentrated to 25 ml. The precipitate obtained on chilling was filtered, dried, and recrystallized from benzene to yield 4.90 g (97%) of Ia, mp 71–72°.

Anal. Calcd for $C_{10}H_{12}N_2O_2$: C, 62.48; H, 6.29; N, 14.58. Found: C, 62.71; H, 6.38; N, 14.42.

The infrared spectrum of this material was identical with that of the material in preparation A above: mmp 70–72°.

(2-Chloroethyl) 3-phenylcarbazate (VI) was prepared, in 67% yield, from 2-chloroethyl chloroformate and phenylhydrazine by the method of Dox:[6] mp 90–91° (lit.[6] mp 89°); infrared (mineral oil mull), 3340, 3210, 1705, 1595, 1545, 1490, 1300, 1280, 1255, 1240, 1180, 1145, 1080, 1070, 1025, 940, 895, 755, and 700 cm^{-1}.

Cyclization of VI. 3-Anilino-2-oxazolidinone (VIII).—Compound VI was treated with sodium ethoxide by the method of Dox[6] to give a 50% yield of VIII: mp 118–120° (lit.[6] mp 120°); infrared (mineral oil mull), 3260, 1745, 1595, 1480, 1460, 1410, 1280, 1240, 1105, 1030, 970, 890, 840, 760, and 700 cm^{-1}.

(2-Chloroethyl) 3-Acetyl-3-phenylcarbazate (IX).—To a solution of 3.0 g (0.02 mole) of 1-acetyl-1-phenylhydrazine[8] in 50 ml of dioxane was added over 10 min a solution of 2.86 g (0.02 mole) of 2-chloroethyl chloroformate in 10 ml of dioxane and a solution of 2.02 g (0.02 mole) of triethylamine in 10 ml of dioxane. After stirring 1 hr at 25°, the solution was refluxed 1 hr and then chilled. Precipitated sodium chloride was filtered and the dioxane was stripped *in vacuo*. Recrystallization of the residue from absolute alcohol gave 2.75 g (54%) of IX, small, white crystals, mp 100–102°.

Anal. Calcd for $C_{11}H_{13}ClN_2O_3$: C, 51.46; H, 5.07; N, 10.92. Found: C, 51.26; H, 5.15; N, 11.17.

3-(N-Acetyl-N-phenylamino)-2-oxazolidinone (X). A. From VIII.—A solution of 1.0 g (0.0056 mole) of VIII in 2 ml of acetic anhydride was refluxed for 18 hr. Acetic acid and excess anhydride were stripped *in vacuo*. The oily residue on standing several days solidified. Recrystallization from benzene–petroleum ether (bp 30–60°) then gave 0.71 g (58%) of white cuboids, mp 67–69°.

Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.72; H, 5.28; N, 12.43.

B. From IX.—Sodium (0.115 g, 0.005 g-atom) in 20 ml of absolute alcohol was added over 10 min to 1.28 g (0.005 mole) of IX in 50 ml of absolute alcohol. A precipitate rapidly formed. The mixture was refluxed 2 hr, chilled, and the sodium chloride was filtered. Extraction of the residue with benzene, followed by stripping of the benzene, gave a white solid. Recrystallization from benzene–petroleum ether yielded 0.67 g (61%) of VIII, mp 67–68°.

The infrared spectrum of this compound was identical with that of the compound in preparation A above: mmp 67–68°.

Grignard Reagents from *t*-Propargylic Chlorides[1]

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It is well known that Grignard reagents are rapidly decomposed by 1-alkynes (as with other active hydrogen compounds) and the mechanisms[2] of such reactions have received careful study. Thus, it may seem surprising that propargyl bromide reacts with magnesium under ether, if a little mercuric chloride is added, to form a Grignard reagent[3] which, in turn, reacts with carbonyl compounds[4] to yield propargylcarbinols, $RR'C(OH)CH_2C{\equiv}CH$. Jacobs and Moore[5] reported that propargyl bromide and chloride and the isomeric haloallenes form the *same* Grignard reagent which has the allenic structure, $CH_2{=}C{=}CHMgX$. Hydrolysis gave allene and methylacetylene (ratio 80:20), while treatment with ketones gave exclusively propargylic products as claimed earlier by Gaudemar.[4]

We describe now many efforts to form Grignard reagents from *t*-propargylic chlorides, $RR'C(Cl)C{\equiv}CH$, which indicated that the reaction with magnesium is considerably more complicated than with propargyl chloride itself. The important observations are as follows. (A) Three *t*-chlorides (R = R′ = CH_3; R = R′ = C_2H_5; and RR′C = cyclohexyl) failed to react with magnesium under ether under all conditions tried, including catalysis with mercuric chloride and Pearson's entrainment method,[6] generally useful with inert halides. (B) Reactions with magnesium proceeded smoothly in tetrahydrofuran (THF) at 40–60° provided the magnesium was activated with mercuric chloride and (in some instances) ethylene dibromide. In all cases the magnesium consumed was appreciably less than theoretical, suggesting that coupling reactions and/or Grignard alkylations were involved. (C) Experiments with 3-chloro-3-methyl-1-butyne (R = R′ = CH_3) included, in one case, distillation prior to hydrolysis or other postreaction; the distillate contained considerable dimethylallene contaminated with isopropylacetylene and traces of isopropenylacetylene. (D) Hydrolysis of freshly prepared crude reaction products, followed by work-up in the usual manner, gave poor yields (not over 50%) of monomeric hydrocarbons found to be mixtures of allene, alkylacetylene, and alkenylacetylene. Higher boiling distillates showed acetylenic, allenic, and conjugate olefinic infrared bands; glpc examination of these fractions showed them to be complex mixtures of coupling products. (E) Attempts to identify specific Grignard reagents

(1) Paper 82 on substituted acetylenes; previous paper, G. F. Hennion and C. V. DiGiovanna, *J. Org. Chem.*, **30**, 3696 (1965).

(2) (a) J. H. Wotiz and G. L. Proffitt, *ibid.*, **30**, 1240 (1965), and earlier papers; (b) H. Hashimoto, T. Nakano, and H. Okada, *ibid.*, **30**, 1234 (1965), and references cited.

(3) C. Prevost, M. Gaudemar, and J. Honigberg, *Compt. Rend.*, **230**, 1186 (1950); *Bull. Soc. Chim. France*, 679 (1959).

(4) M. Gaudemar, *Compt. Rend.*, **233**, 64 (1951); *Ann. Chim.* (Paris), [13] **1**, 161 (1956).

(5) T. L. Jacobs and T. L. Moore, Abstracts of Papers, 141st Meeting of the American Chemical Society, Washington, D. C., March, 1962, p. 19-O.

(6) D. E. Pearson, D. Cowan, and J. D. Beckler, *J. Org. Chem.*, **24**, 504 (1959).