Synthesis of 4-Phenyl-1H-2,3-benzoxazine. A Convenient Route to a Rare Class of Compounds[1]

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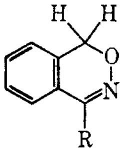
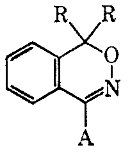
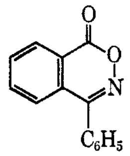
4-Phenyl-1H-2,3-benzoxazine, which is the first example of this type of compound having no substituent at the 1 position, was synthesized in four convenient steps from N,N-dimethylbenzylamine and benzonitrile. The final step, which involves cyclization of the lithio salt of a methiodide oxime, is presumably made possible by isomerization of the *cis* oxime salt to its *trans* isomer. The method should be applicable to ring-substituted N,N-dimethylbenzylamines and other aryl nitriles. An attempt to prepare the unsubstituted parent compound, 1H-2,3-benzoxazine, was unsuccessful.

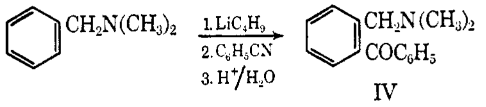
1,2-Oxazines in general are not well known in the literature,[2] and no benzoxazine of type I, which has no substituent at the 1 position, appears to have been described previously. Moreover, only one substituted benzoxazine of type I has been reported; the preparation of this compound, II (R, A = C_6H_5), involved treatment of the keto compound III with phenylmagnesium bromide and cyclization of the resulting carbinol oxime with hydrochloric and acetic acids.[3] Also, the "oxime" of phenolphthalein has been suggested to have structure II (R = 4-hydroxyphenyl, A = hydroxyl).[4]


I


II

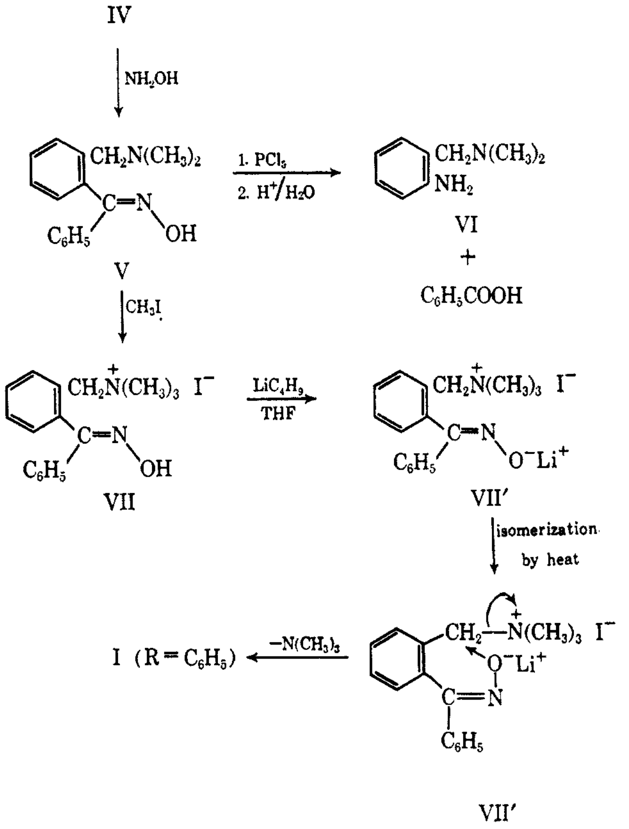

III

Since ketoamine IV is readily available from N,N-dimethylbenzylamine and benzonitrile,[5] it seemed possible to prepare the benzoxazine I (R = C_6H_5) by oximation of the ketone group and methylation of the amine group of IV, followed by a base-catalyzed cyclization. This was realized in the present investigation.



The method of preparation of the benzoxazine I (R = C_6H_5) from ketoamine IV, and the establishment of the structure of the intermediate oxime through a Beckmann rearrangement, are indicated in Scheme I.

SCHEME I



The intermediate oxime evidently has structure V since Beckmann rearrangement with phosphorous pentachloride afforded an amide, which yielded N^α,N^α-dimethyltoluene-α,2-diamine (VI) and benzoic acid on hydrolysis.[6] The methiodide oxime VII, obtained as the sole methylation product, presumably had the same configuration, in which the hydroxyl and phenyl groups are *cis*. Since these groups must be *trans* in order for cyclization to occur, the *cis*-lithio salt VII′ apparently isomerized to the *trans*-lithio salt VII″ which underwent cyclization to give the benzoxazine I (R = C_6H_5). The yields from the oximation of ketoamine IV and the methylation of the resulting oxime V were excellent, and that from the cyclization was good; the over-all yield (based on IV) of I (R = C_6H_5) was 56%.

It can readily be seen that the method of preparation of I (R = C_6H_5) should provide a convenient route to several other new 1H-2,3-benzoxazines by employment of appropriately substituted N,N-dimethylbenzylamines and/or of other aryl nitriles. The method may also be suitable for the preparation of certain alkyl derivatives of I.

It should be mentioned that an attempt to prepare the methiodide oxime VII by reaction of the methiodide of ketoamine IV with hydroxylamine was unsuccessful; only starting material was recovered. Similarly, this methiodide was found to be unreactive toward phenylhydrazine. This failure can probably be ascribed to a steric factor.

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[1] Supported by Public Health Service Research Grant No. CA-04455 from the National Cancer Institute.

[2] See R. L. McKee in "The Chemistry of Heterocyclic Compounds," Vol. 17, A. Weissberger, Ed., "Five- and Six-Membered Compounds with Nitrogen and Oxygen (Excluding Oxazoles)," R. H. Wiley, Ed., Interscience Publishers, Inc., 1962, Chapter 13.

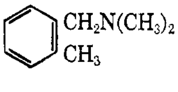
[3] A. Mustafa, W. Asker, M. Kamel, A. F. A. Shalaby, and A. E. A. E. Hassan, *J. Amer. Chem. Soc.*, **77**, 1612 1955).

[4] H. Lund, *Acta Chem. Scand.*, **8**, 1307 (1954).

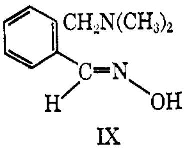
[5] F. N. Jones, R. L. Vaulx, and C. R. Hauser, *J. Org. Chem.*, **28**, 3461 (1963).

[6] L. G. Donaruma and W. Z. Heldt, *Org. Reactions*, **11**, 54 (1960).

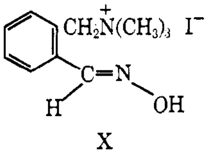
Next, an attempt was made to prepare the benzoxazine I (R = H) by cyclization of the methiodide oxime X; the latter was prepared by methylation of the amino oxime IX which, in turn, was obtained by lithiation of amine VIII with *n*-butyllithium and treatment of the resulting lithioamine with *n*-butyl nitrite. However, treatment of the methiodide oxime X with *n*-butyllithium in tetrahydrofuran (THF) followed by heating (conditions used with VII) resulted in a substantial recovery of X together with trace amounts of other materials (probably arising by decomposition of the lithio salt of X). When the higher boiling solvent di-*n*-butyl ether was used, even more intractable materials were obtained.



VIII



IX



X

Experimental Section

All infrared spectra were measured as mulls in Nujol and hexachlorobutadiene unless otherwise stated, using a Perkin-Elmer spectrophotometer (Model 137). The ^1H nmr spectra were measured using a Varian A-60 spectrometer with tetramethylsilane as internal standard. Microanalyses were carried out by Jannsen Pharmaceutica, Beerse, Belgium, and also by M-H-W Laboratories, Garden City, Mich. Melting points were recorded on a Thomas-Hoover capillary melting point apparatus and are uncorrected.

Preparation of 2-(Dimethylaminomethyl)benzophenone (IV).—This was effected by using N,N-dimethylbenzylamine, *n*-butyllithium,[7] and benzonitrile, essentially as described previously.[5] Product IV recrystallized from hexane (charcoal) as large colorless prisms: mp 46–47° (lit.[5] mp 45–46°); ν_{max} 1660 (C=O), 1445, 1307, 1268, 1245, 928, 763, 737, 702 cm^{-1}.

Reaction of IV with Hydroxylamine to Form V.—A solution of hydrated sodium acetate (23.2 g, 0.17 mol) in water (50 ml) was added to a warm solution of IV (34.0 g, 0.14 mol) and hydroxylamine hydrochloride (11.9 g, 0.17 mol) in 95% ethanol (150 ml); the resulting solution was then boiled under reflux for 4 hr, cooled, and poured into stirred water (500 ml). The aqueous solution was neutralized with sodium bicarbonate and extracted with three 200-ml portions of ether. The dried ($MgSO_4$) ether solution was evaporated to provide a creamish solid (33.10 g, 92%) which, on crystallization from acetonitrile, provided the pure oxime (27.93 g, 77%) as colorless prisms: mp 126–128°; ν_{max} 2775 broad (OH), 1440, 1000, 934, 854, 770, 734, 695, 689 cm^{-1}; nmr ($CDCl_3$), τ −0.38 (broad singlet, hydroxyl), 2.14–3.02 (multiplet, aromatic), 6.64 (singlet, methylene), 7.86 (singlet, methyl), area ratio 1:9:2:6.

Anal. Calcd for $C_{16}H_{18}N_2O$: C, 75.56; H, 7.13; N, 11.02. Found: C, 75.78; H, 7.16; N, 10.82.

Beckmann Rearrangement of V.—Phosphorous pentachloride (6.24 g, 0.03 mol) was added to a stirred solution of the finely divided oxime (5.08 g, 0.02 mol) in dry ether (200 ml) at 0°, to give a white suspension. The suspension was allowed to warm to room temperature during 0.5 hr and then stirred for a further 3 hr; during this time a clear solution which contained a greenish gum was obtained. The mixture was then poured, with stirring, into ice and water (300 g) to provide a clear solution. The colorless ether layer was separated, dried ($MgSO_4$), and evaporated, but no solid was obtained. The pale green aqueous layer was neutralized ($NaHCO_3$) when a yellowish oil separated and was extracted with ether (200 ml, then 100 ml). Evaporation of the dried ($MgSO_4$) ether solution afforded a viscous yellow oil (2.54 g) which could not be induced to crystallize. A further quantity of the oil (0.36 g) was obtained by concentration of the aqueous layer to *ca.* 60 ml and extraction with ether (100 ml, then 50 ml) as before. The total yield of the product was thus 2.90 g (57%). The infrared spectrum (liquid film) was consistent with that expected for a N-aryl-substituted benzamide, *e.g.*, ν_{max} 3200 (NH), 1660 (C=O).

The oil (2.40 g) was dissolved in 65% sulfuric acid (30 ml) and the solution was boiled under reflux for 2 hr; during this time benzoic acid vaporized and solidified in the condenser and was thus washed back into the solution with hot water (30 ml). When chilled overnight, the solution deposited a pale gray solid (0.49 g, 43%) which, on recrystallization from water, furnished benzoic acid (0.35 g, 30%) as colorless leaves, mp 121.5–122°.

The pale yellow filtrate was basified (cooling) with 10% sodium hydroxide solution and extracted with two 50-ml portions of ether. Evaportion of the dried ($MgSO_4$) ether solution yielded a brownish orange oil (0.47 g) which crystallized when chilled. The brown color was removed by pressing the solid between filter papers, leaving N^{α},N^{α}-dimethyltoluene-α,2-diamine (0.20 g, 14%) as colorless needles: mp 37–37.5° (lit.[8] mp 36–37°); ν_{max} 3445 (NH), 3310 (NH), 1615 (NH), 1495, 1455, 1285, 1020, 751 cm^{-1}.

Anal. Calcd for $C_9H_{14}N_2$: C, 71.95; H, 9.39; N, 18.65. Found: C, 71.48; H, 9.27; N, 18.25.

Reaction of V with Methyl Iodide.—Methyl iodide (12.42 g, 0.087 mol) was added during 4 min to a stirred suspension of V (18.5 g, 0.073 mol) in absolute ethanol (200 ml). After being stirred for a further 6 min at room temperatue, the suspension was boiled under reflux for 20 min when V dissolved. The cooled solution was poured, with stirring, into ether (700 ml) and the resulting white precipitate was collected and dried. Product VII (26.13 g, 91%) crystallized, with chilling, from acetonitrile to give the pure methiodide (23.89 g, 83%) as colorless acicular plates, mp 212–216° dec with darkening above 170°.

Anal. Calcd for $C_{17}H_{21}IN_2O$: C, 51.51; H, 5.30; I, 32.07; N, 7.07. Found: C, 51.72; H, 5.57; I, 32.38; N, 6.91.

Cyclization of VII to Give 4-Phenyl-1H-2,3-benzoxazine (I, R = C_6H_5).—A slight excess of a *ca.* 1.6 *M* solution of *n*-butyllithium in hexane (6.7 ml) was added dropwise over 5 min to a pale yellow suspension of VII (3.96 g, 0.01 mol) in dry THF (100 ml) at 0° under nitrogen; the suspension became colorless initially and then orange. After being stirred for a further 15 min at 0° without evolution of trimethylamine, the suspension was heated to reflux temperature during 30 min. Trimethylamine was now evolved and the reaction mixture was boiled under reflux until evolution of the gas had ceased (20 hr). During this time the color of the suspension became paler; after *ca.* 0.75 hr it was pale yellow, whereas after *ca.* 1.5 hr a green color developed.

The dark green suspension was filtered while hot to remove a small amount of a colorless (when washed with 10 ml of dry THF) solid which was largely water soluble and gave a positive test for iodide ion; this was presumably lithium iodide or recovered VII. Evaporation of the filtrate gave a dark green tar which could not be induced to solidify and was thus dissolved in the minimum volume of dry benzene and chromatographed on alumina (Fischer, 80–200 mesh). The colorless first fraction (which was sometimes eluted as a bluish green band) was eluted with a 1:1 mixture of petroleum ether (bp 30–60°) and benzene and then benzene, and, on evaporation, it afforded a dark green oil. This oil solidified on standing to provide a pale green solid (1.41 g, 67%) which, by two recrystallizations from hexane-benzene, furnished 4-phenyl-1H-2,3-benzoxazine (1.06 g, 51%) as clusters of colorless acicular plates: mp 76.5–77°; ν_{max} 1325, 1105 broad, 981, 860, 780, 760, 719, 696 cm^{-1}; nmr ($CDCl_3$), τ 2.17–3.00 (multiplet, aromatic), 5.05 (singlet, methylene), ratio 9:2.

Anal. Calcd for $C_{14}H_{11}NO$: C, 80.36; H, 5.30; N, 6.69. Found: C, 80.61; H, 5.39; N, 6.59.

Evaporation of the other eluted fractions yielded small quantities of tarry materials together with lithium iodide; the latter was eluted with ethanol-methanol mixtures.

Attempted Reaction of the Methiodide of IV with Hydroxylamine.—A sample of ketoamine IV was treated with methyl iodide in absolute ethanol to form the methiodide: mp 175° dec with gradual darkening above 160° (lit.[5] mp 175° dec); ν_{max} 1670 (C=O), 1280, 1250, 934, 914, 894, 785, 777, 720 cm^{-1}.

To a warm solution of the methiodide (7.92 g, 0.02 mol) and hydroxylamine hydrochloride (1.30 g, 0.02 mol) in 95% ethanol (50 ml) was added a solution of hydrated sodium acetate (2.72 g, 0.02 mol) in water (10 ml). The resulting solution was boiled under reflux for 30 min, then allowed to cool. Filtration of the

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[7] Used as supplied by Foote Mineral Co., Exton, Pa.

[8] E. Stedman, *J. Chem. Soc.*, 1902 (1927).

chilled reaction mixture furnished colorless crystals (1.89 g) and two more crops (total 5.13 g) were subsequently obtained from the filtrate. These crystals were identified as the starting methiodide of IV (65% recovery) by melting point and infrared spectrum.

Other reactions for longer periods or in the absence of hydrated sodium acetate gave similar results.

An attempted reaction between the methiodide of IV and phenylhydrazine in refluxing absolute ethanol which contained glacial acetic acid, resulted in an 88% recovery of the methiodide.

Reaction of *o*-N,N-Trimethylbenzylamine (VIII) with *n*-Butyllithium and *n*-Butyl Nitrite.—A slight excess of a *ca.* 1.6 *M* solution of *n*-butyllithium in hexane (267 ml) was added to a stirred solution of VIII[9] (59.6 g, 0.4 mol) in dry ether (100 ml) under nitrogen; after 2–3 hr, a cream-colored precipitate separated. The mixture was stirred at room temperature for 18 hr, during which time more dry ether was added to make up for losses by evaporation. The suspension was then added during 40 min to freshly prepared *n*-butyl nitrite[10] (20.6 g, 0.2 mol) at 0° to give an orange suspension initially which, toward the end of the addition, changed to a deep red solution; stirring at 0° was continued for a further 1 hr. The reaction mixture was poured into stirred water (200 ml) and the brown aqueous layer separated from the brown organic layer, acidified (glacial acetic acid), and neutralized ($NaHCO_3$). Extraction with three 200-ml portions of ether and evaporation of the dried ($MgSO_4$) ether layer furnished a viscous brown oil (10.64 g, 28%) whose infrared spectrum (liquid film) was consistent with that expected for the required oxime (IX): ν_{max} 3220 (OH), 2940 and 2850 (aliphatic CH), 1455, 1175, 1098, 1020, 965, 841, 758 cm^{-1}. This oil could not be induced to crystallize and was thus allowed to react with methyl iodide directly.

Reaction of the Crude Oxime (IX) with Methyl Iodide.—Methyl iodide (2.85 g, 0.020 mol) was added during 1 min to a stirred solution of the crude oxime IX (3.25 g, 0.018 mol) in absolute ethanol (30 ml) and, after *ca.* 50 min, a solid precipitated. The reaction mixture was stirred for a further 70 min and then filtered to give the crude methiodide (3.29 g); a further crop (0.52 g) was obtained by dilution of the filtrate with ether (400 ml); thus the total yield was 3.81 g (65%). Crystallization, with chilling, afforded the pure quaternary methiodide X (2.88 g, 49%) as colorless acicular plates: mp 196° dec with gradual darkening above 160°; ν_{max} 3240 (OH), 1477, 1407, 1370, 1285, 977, 961, 896, 888, 780, 763, 720 cm^{-1}.

Anal. Calcd for $C_{11}H_{17}IN_2O$: C, 41.26; H, 5.35; I, 39.64; N, 8.75. Found: C, 41.12; H, 5.44; I, 39.81; N, 8.60.

Attempted Cyclization of X.—A slight excess of a *ca.* 1.6 *M* solution of *n*-butyllithium in hexane (6.7 ml) was added during 5 min to a white suspension of X (3.20 g, 0.01 mol) in dry THF (100 ml) at 0° under nitrogen; the suspension became reddish brown and finally brown. Trimethylamine was evolved, and the solution was stirred at 0° for 15 min and allowed to warm to room temperature. After 16 hr trimethylamine was still being evolved; after making up the loss of solvent by evaporation, the suspension was boiled under reflux for 24 hr with the addition of more dry THF (50 ml) during this time. Although trimethylamine was still being evolved, the chocolate-colored suspension was allowed to cool and then filtered to provide a sticky brown solid (2.66 g) whose infrared spectrum showed it to be crude recovered X. Evaporation of the filtrate gave a reddish brown oil (1.25 g) which was chromatographed on alumina (Fischer, 80–200 mesh). Six different fractions were eluted, but each one yielded only an intractable tar on evaporation (total amount of tar, 0.75 g).

A second reaction, using di-*n*-butyl ether as solvent, gave similar results (probably owing to decomposition of the lithio salt of X).

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[9] W. R. Brasen and C. R. Hauser, *Org. Syn.*, **34**, 61 (1954).

[10] W. A. Noyes, *ibid.*, **16**, 7 (1936).

Aminimides. VI.[1a,b] Synthesis of Aminimides from Carboxylic Acid Esters, Unsymmetrically Disubstituted Hydrazines, and Epoxides

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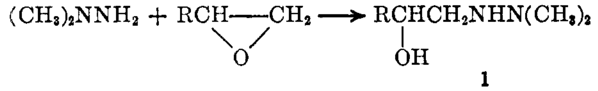
The reaction of unsymmetrically disubstituted hydrazines, epoxides, and carboxylic acid esters gives 1,1-disubstituted 1-(2-hydroxyalkyl- or aryl-)aminimides in excellent yields. Evidence is presented to support a primary reaction between the hydrazine and the epoxide to give an aminimine which subsequently reacts with the ester to give the aminimide. The aminimide may be pyrolyzed to give an isocyanate and a β-hydroxy tertiary amine which subsequently react to form a urethan.

Very little mention is made in the literature concerning the reaction between unsymmetrically substituted hydrazines and epoxides. In fact, only two references[2,3] could be found, both of which support the attack of the unsubstituted nitrogen on the terminal epoxide carbon atom (eq 1).



(1)

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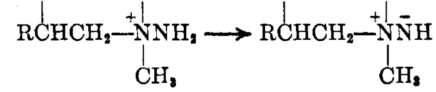
It seemed more logical to us that the more nucleophilic substituted nitrogen would attack the epoxide to give the hydrazinium alkoxide 2 (eq 2). It is known from prior work[4] that alkoxides react with 1,1,1-trisubstituted hydrazinium salts to give aminimines. If 2 is formed, then it is logical to assume an extraction of a nitrogen proton by the alkoxide to provide the aminimine 3.



(2)

2 3

Results and Discussion

Since it was known[5,6] that aminimines react with carboxylic acid esters to produce aminimides, we tested

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[1] (a) For paper V in this series, see B. M. Culbertson, E. A. Sedor, S. Dietz, and R. E. Fries, accepted for publication in *J. Polymer Sci., Part A-1.* (b) Presented at the 155th National Meeting of the American Chemical Society, San Francisco, Calif., 1968. (c) Current address is Calgon Corp., Calgon Center, Box 1346, Pittsburgh, Pa. 15230.

[2] F. Ya. Perveev and V. Ershova, *Zh. Obshch. Khim.*, **30**, 3554 (1960).

[3] G. Benoit, *Bull. Soc. Chim. Fr.*, **6**, 708 (1939).

[4] R. Appel, H. Heinen, and R. Schollhorn, *Chem. Ber.*, **99**, 3118 (1966).

[5] H. W. Schiessl and R. Appel, *J. Org. Chem.*, **31**, 3851 (1966).

[6] W. J. McKillip and R. C. Slagel, *Can. J. Chem.*, **45**, 2619 (1967).