The same compound was obtained by treatment of the dihydrochloride with trimethylamine, followed by oxidation of the free base with activated manganese dioxide[13] in dimethyl ether. This gave a crude sample of 1,2-diazacycloocta-1,5-diene which was distilled from a water bath at 10° to a receiver held at −78°. Without further purification of the free azo compound, treatment with a saturated solution of Cu_2Cl_2 in 10% HCl gave the same complex described above, identified by infrared spectral comparison.

Registry No.—**3,** 34201-71-3; **5** hydrochloride, 34201-72-4; **5** dihydrochloride, 34201-73-5; **6,** 11089-64-8; **7,** 34201-74-6; **9,** 34201-75-7; 1,2-diazacyclooctane monohydrochloride, 34201-76-8; 1,2-diazacyclooctane dihydrochloride, 34201-77-9.

Acknowledgment.—Thanks are due to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this work.

[13] L. A. Carpino, *J. Org. Chem.*, **35**, 3971 (1970).

A Study of the Cyclization of 2′-Formamido-4′,5′-dimethoxypropiophenone with Ammonia

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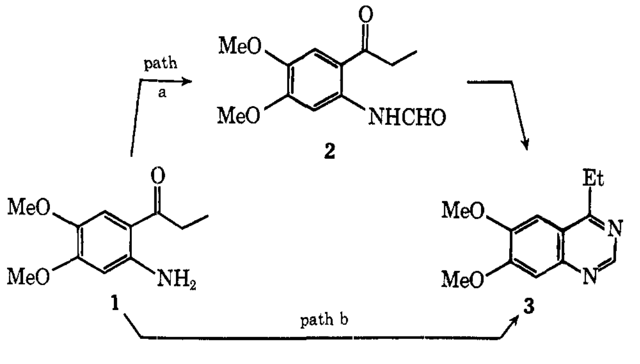
The compound [2-^{14}C]-6,7-dimethoxy-4-ethylquinazoline was required for metabolism studies. Scheme I shows the general approach considered for its synthesis.

Scheme I



Previously, 6,7-dimethoxy-4-ethylquinazoline[1] (**3**) was prepared in these laboratories by formylation of 2′-amino-4′,5′-dimethoxypropiophenone[2] (**1**) with excess mixed formic–acetic anhydride, followed by heating the resulting 2′-formamido-4′,5′-dimethoxypropiophenone (**2**) in fused ammonium formate saturated with ammonia (path a),[3] or by heating **1** with formamide and formic acid (path b).[4] Compound **3** labeled at the 2 position could be made *via* path a if methods for the efficient incorporation of a [^{14}C]formyl group could be found. Certainly, the methods used previously for the conversions **1** to **2** or **1** to **3** would not be suitable because of the excesses of formic acid or formic acid derivatives used in each case. The synthesis of [^{14}C]formyl-**2** was easily accomplished by reaction of **1** with 1 equiv each of [^{14}C]formic acid and dicyclohexylcarbodiimide (DCC).

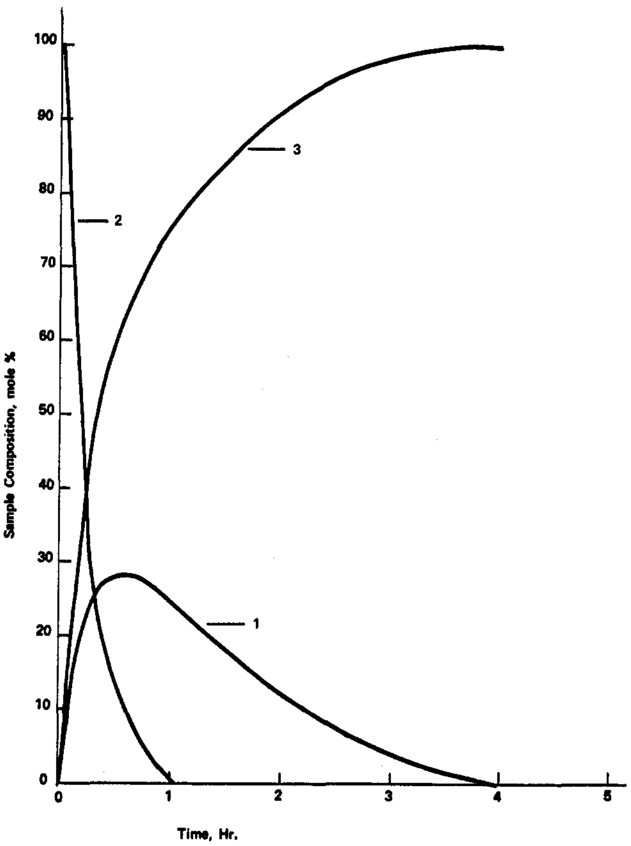


Figure 1.—The reaction of **2** with ammonia in ammonium formate at 125°. Mole per cent composition of the reaction mixture *vs.* time.

The question remaining concerned the fate of the label in **2**. Would it be lost in the conversion of **2** to **3**? The course of this reaction was studied by adding **2** with stirring to fused ammonium formate saturated with ammonia at 125° and withdrawing aliquots periodically. The samples were analyzed by glc, and the results are presented in Figure 1, in which the mole per cent composition of the sample is plotted against reaction time. Figure 1 indicates that **2** may proceed to **3** irreversibly, and/or it may equilibrate with **1**. Complete conversion to **3** is assured by the fact that it is formed essentially irreversibly. This experiment showed that ring closure of labeled **2** under these conditions would lose the label to the reaction medium.

As an alternate to the ring closure in fused ammonium formate, the reaction of **2** in ethanol saturated with ammonia in a sealed tube was investigated. The results of reactions at various temperatures and for various times are presented in Table I. It should be noted that here again the starting formanilide **2** equilibrates with the amine **1**, but the formic acid is captive and does not equilibrate with solvent.

In the actual synthesis of the labeled compound, using 23.5 mCi of [^{14}C]formic acid, in the DCC formylation procedure, 2′-formamido[^{14}C]-4′,5′-dimethoxypropiophenone was obtained, after recrystallization from methanol, in 82.8% yield. This material was

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[1] The U. S. Adopted Name for this material is Quazodine.

[2] D. E. Ames and A. C. Lovesey, *J. Chem. Soc.*, 6306 (1965).

[3] J. L. Minielli and H. C. Scarborough, U. S. Patent 3,248,292 (1966).

[4] S. Palazzo, *Boll. Sedute Accad. Gioenia Sci. Natur. Catania*, **71**, 75 (1959); *Chem. Abstr.*, **55**, 12412 (1961).

TABLE I

REACTION OF 2 WITH AMMONIA IN ETHANOL

Time	Temp, °C	Sample composition, %			
		1	2	3	Unidentified
2 weeks	25	7.2	11.1	81.9	0
4 hr	100	5.2	29.9	65.0	0
4 hr	150	11.8	14.3	73.9	0
8 hr	150	6.8	0	84.4	8.8
12 hr	150	7.7	0	89.6	2.7

then cyclized to [2-^{14}C]-6,7-dimethoxy-4-ethylquinazoline by heating the formamido compound in a sealed tube with ethanol and ammonia at 150° for 12 hr. The residue from the reaction was recrystallized from acetone to give (in two crops) the product in 63% yield. The two crops were combined with unlabeled material by recrystallization. The total ^{14}C content was 6.41 mCi, which, allowing for the material recovery, amounts to 56.4% incorporation of the [^{14}C]formic acid.

Experimental Section

6,7-Dimethoxy-4-ethylquinazoline (3). Ammonium Formate Method.—A 100-ml three-necked flask equipped with a magnetic stirrer, gas inlet tube, thermometer, and condenser was charged with 25.2 g (0.4 mol) of ammonium formate. The ammonium formate was heated to 125° with stirring. Then 2.37 g (0.01 mol) of 2 (*vide infra*) was added; the addition of ammonia gas below the surface at a moderate rate was started immediately. Periodically, 0.1-ml samples were withdrawn, diluted with 5 ml of water, adjusted to pH 9 with NH_4OH, and extracted with $CHCl_3$ (5 ml). The extracts were analyzed by glc;[5] the results are presented in Figure 1. After 6 hr of reaction, the mixture was poured into water, made basic with NH_4OH, and extracted with $CHCl_3$. The extract was dried ($MgSO_4$) and evaporated *in vacuo* to give a yellow solid. The solid was recrystallized from acetone–hexane to give 1.5 g (69%) of white product, mp 149–150.5°.

6,7-Dimethoxy-4-ethylquinazoline (3). Ammonia in Ethanol Method.—A solution of 0.5 g (2.11 mmol) of 2 in 75 ml of absolute EtOH was saturated with ammonia at 0° in a steel cylinder of 100-ml capacity. The bomb was sealed and heated to temperature and held there for a specified time. After the reaction period the cylinder was cooled and opened, and the solution was analyzed by glc without further treatment.[5] The results of several runs are presented in Table I. The solution was then evaporated to dryness, and the residue was recrystallized from acetone–hexane to give white crystalline material.

2′-Formamido[^{14}C]-4′,5′-dimethoxypropiophenone.—A 100-ml three-necked flask equipped with a mechanical stirrer, thermometer, and addition funnel was charged with 2.30 g (11.0 mmol) of 2 and 0.515 g of 97% formic acid (11.0 mmol of anhydrous HCO_2H). Then 23.5 mCi of [^{14}C]formic acid (specific activity 60 mCi/mmol) was transferred to the flask with 30 ml of CH_2Cl_2. A solution of 2.44 g (11.83 mmol) of dicyclohexylcarbodiimide in 30 ml of CH_2Cl_2 was added over 5 min, during which time the temperature was maintained at 20–25° with an ice bath. The mixture was stirred at room temperature for 1 hr, and then the dicyclohexylurea was filtered, rinsed with CH_2Cl_2, and air dried to give 2.5 g (100% of theory) of white material. The combined filtrates were evaporated *in vacuo*, and the residue was recrystallized from 15 ml of MeOH. The material was filtered, rinsed with MeOH, and air dried to give 2.16 g (82.8%) of slightly yellow material, mp 125–130°. The material was carried directly to the next step.

[2-^{14}C]-6,7-Dimethoxy-4-ethylquinazoline.—A cylindrical stainless steel pressure vessel of 100-ml capacity was charged with 2.16 g (9.12 mmol) of 2′-formamido[^{14}C]-4′,5′-dimethoxypropiophenone and 75 ml of absolute EtOH. The mixture was cooled and saturated with NH_3. The vessel was sealed and heated at 150° for 12 hr; it was then cooled and opened. The content was evaporated *in vacuo* to dryness. The residue was taken up in 75 ml of hot acetone, treated with Darco G-60 charcoal, and concentrated *in vacuo* to 25 ml. The solution was cooled, and the precipitate was filtered, rinsed with cold acetone (2 × 3 ml), and air dried to give 0.96 g of material. The combined filtrates were treated with charcoal and evaporated *in vacuo*. The residue was recrystallized from 5 ml of acetone to give 0.26 g of product. The two crops (total 1.22 g, 63%) were combined with 1.225 g of 3, and the whole was dissolved in 30 ml of acetone. The solution was concentrated to 20 ml and cooled. The solid was filtered and air dried to give 2.275 g of off-white solid (92.9% recovery), mp 149–150°, specific activity 2.82 μCi/mg.[6] The thin layer radiochromatogram showed one spot.[7]

Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.83. Found: C, 65.83; H, 6.46; N, 12.86.

Registry No.—2, 34314-99-3; 3, 4015-32-1; 2′-formamido[^{14}C]-4′,5′-dimethoxypropiophenone, 34314-79-9; [2-^{14}C]-6,7-dimethoxy-4-ethylquinazoline, 34315-01-0.

Acknowledgments.—I am indebted to Dr. J. A. LaBudde and his group for the tlc and activity count, and to Mr. C. Combs and his group for the elemental analysis.

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[5] The glc analyses were made using 1.2 m × 6 mm dual glass columns packed with 3.8 wt % UC W-98 on 80/100 mesh Diatoport S; the oven temperature was programmed from 150 to 250° at 10°/min. The flow rates in ml/min were He, 40; H_2, 20; and air, 300; and the detector was a dual flame-ionization model. The retention times (in min) were **4**, 4.55; **5**, 5.90; and **6**, 5.30; respectively. All the components were assumed to have the same response; and, consequently, the area per cent is taken as mole per cent composition of the sample.

[6] The radioactivity of the samples was determined in a Packard Tri-Carb liquid scintillation counter in a counting solution of 2.5-diphenyloxazole (7 g/l.) and naphthalene (100 g/l. in *p*-dioxane).

[7] The tlc was run by spotting the sample from chloroform on Eastman No. 6060 silica gel tlc sheet and eluting with 50:50 Skelly F/acetone. The eluted strips were scanned with a Varian Aerograph Berthold radioscanner which showed a single radioactive peak.

Stereoselective Synthesis of Racemic Grandisol

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Grandisol (**1a**) is one of the four components of the boll weevil sex pheromone and has been previously synthesized nonselectively[1] and stereoselectively.[2] We now report another stereoselective synthesis which provides gram quantities of pure **1a**.

Since ethylene undergoes 2 + 2 cycloaddition in the required cis manner to negatively substituted cyclohexenones[3] which are photochemically activated, we attempted the addition of ethylene to 5,6-dihydro-4-methyl-2*H*-pyran-2-one[4] (**2**).

Indeed, when **2** was irradiated in benzene saturated and continuously swept with ethylene, the bicyclic lactone, 6-methyl-3-oxabicyclo[4.2.0]octan-2-one (**3**), was the major product. The reaction proceeds *via* a

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[1] (a) J. H. Tumlinson, D. D. Hardee, R. C. Gueldner, A. C. Thompson, P. A. Hedin, and J. P. Minyard, *Science*, **166**, 1010 (1969); (b) J. H. Tumlinson, R. C. Gueldner, D. D. Hardee, A. C. Thompson, P. A. Hedin, and J. P. Minyard, *J. Org. Chem.*, **36**, 2616 (1971).

[2] R. L. Zurflüh, L. L. Dunham, V. L. Spain, and J. B. Siddall, *J. Amer. Chem. Soc.*, **92**, 425 (1970).

[3] W. C. Agosta and W. W. Lowrance, Jr., *Tetrahedron Lett.*, 3053 (1969). We are grateful to W. C. Agosta for providing a preprint.

[4] (a) A. L. Remizov and G. A. Tsetkova, *Chem. Abstr.*, **65**, 614*a* (1966); (b) Cornforth, *et al.*, *Tetrahedron*, **5**, 311 (1959).