say, the volume of diluent placed in the mixing reservoir should at least equal the volume of eluate to be collected. Furthermore, if the total volume of solution leaving the reservoir exceeds twice the original volume in the reservoir, the gradient effect of any further elution is negligible.

A more limited form of expression for gradient elution was derived empirically by Donaldson, *et al.*,[3] from experimental data.

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Synthesis of Pentaquine Labeled in the Quinoline Ring with N^{15} [1]

BY ROBERT C. ELDERFIELD,[2] LELAND L. SMITH AND ELEANOR WERBLE

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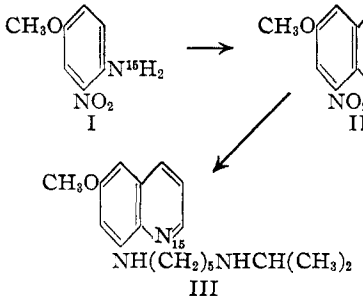
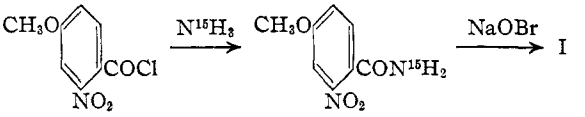
In the preceding paper the preparation of pentaquine [6-methoxy-8-(5-isopropylaminopentylamino)-quinoline] carrying N^{15} in each of the two side chain positions was described.[3] The results of a study of the excretion products of these two labeled drugs when fed to monkeys are described in an accompanying article.[4] In view of the inconclusive nature of the latter studies insofar as the physiological disposition of the drug is concerned, it was felt that a similar study of pentaquine labeled with N^{15} at the quinoline nitrogen was mandatory and might be productive of more useful information. Accordingly we wish to report at this time the synthesis of this substance. The physiological studies with the drug are under way and will be reported in a later communication.

The obvious route to the synthesis of the desired drug involves preparation of 4-methoxy-2-nitroaniline (I) carrying N^{15} in the amino group. By conventional methods 6-methoxy-8-nitroquinoline (II)[5,6] and pentaquine (III)[7] labeled at the ring nitrogen are then easily available.



A logical means for the introduction of N^{15} into I appeared to be at hand in the reaction of 4-methoxy-2-nitrochlorobenzene (IV) with potassium phthalimide enriched with N^{15}. In preliminary experiments *o*-nitrochlorobenzene reacted in good yield with potassium phthalimide in boiling dimethylformamide to yield *o*-nitroaniline after hydrolysis. However, when the same reaction was attempted with IV, the deactivating effect of the methoxyl group was sufficiently great that the analogous reaction was completely prevented. Use of higher boiling solvents or substitution of bromine or iodine for the chlorine in IV were without effect. Therefore another route to I was employed as shown by the formulas



Pentaquine monophosphate was obtained in overall yield of 25% from V by this procedure.

p-Toluidine was nitrated according to Nolting and Collin[8] to yield 4-amino-2-nitrotoluene in 65% yield. This was diazotized to 4-hydroxy-2-nitrotoluene (VI)[9] in 36% yield. Methylation of VI with dimethyl sulfate[9] gave 4-methoxy-2-nitrotoluene in 88% yield. Permanganate oxidation of the latter according to Ullmann and Dootson[10] gave 4-methoxy-2-nitrobenzoic acid. Action of N^{15}-ammonia on the acid chloride of 4-methoxy-2-nitrobenzoic acid gave the amide, m.p. 160–162° from aqueous alcohol. (*Anal.* Calcd. for $C_8H_8N_2O_4$: C, 49.0; H, 4.1; N (normal N), 14.3. Found: C, 48.19; H, 4.4; N, 14.3, 14.6). By degradation of the amide with sodium hypobromite I was obtained in 66% yield.

The pentaquine monophosphate was enriched by 19.6 atoms % excess N^{15}.[11]

(1) The work here reported was done under a grant from the National Institutes of Health to Columbia University.

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(4) R. C. Elderfield and L. L. Smith, *ibid.*, **75**, 1022 (1953).

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(11) The isotopic nitrogen analysis was done by Dr. D. Rittenberg of the College of Physicians and Surgeons of Columbia University to whom we wish to express our appreciation.

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Synthesis of Pentaquine Labeled in the Side Chain with N^{15} [1]

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In order to permit the study of the physiological disposition of pentaquine [6-methoxy-8-(5-isopropylaminopentylamino)-quinoline (I)] described by Elderfield and Smith[2] we prepared samples of pentaquine in which (a) the terminal nitrogen atom of the side chain and (b) the nitrogen atom attached to the 8 position of the quinoline ring was labeled with N^{15}. (For convenience these substances are designated pentaquine-N^{15}(T) and pentaquine-N^{15}(8), respectively.) The synthesis of the third isomer, in which the ring nitrogen atom is

(1) The work reported in this note was done under a grant from the National Institutes of Health to Queens College.

(2) R. C. Elderfield and L. L. Smith, THIS JOURNAL, **75**, 1022 (1953).