remainder fractionated under vacuum to produce 110 g. (90% yield) of a white viscous liquid, b.p. 132–134° (4.5 mm.). The liquid, when dissolved in the minimum amount of dry ether and cooled to Dry Ice temperatures, deposited as a solid which melted over a wide range up to room temperature.

Anal. Calcd. for $C_9H_{18}O_2$: C, 62.04; H, 10.41. Found: C, 61.94; H, 10.60.

Catalytic Treatment of VII.—On heating 87 g. (0.5 mole) of the diol VII with 2.6 g. (3%) of the catalyst, hydrogen was rapidly evolved and a two-phase material distilled. When hydrogen no longer evolved, the remainder in the pot was distilled at vacuum. Refractionation at 0.5 mm. gave 20 g., b.p. 42–44°, and 40 g., b.p. 68–105°. Infrared spectrum indicated that the lower boiling fraction had a double bond contaminated with some carbonyl, and that the higher boiling fraction was a carbonyl compound. A satisfactory analytical sample of the olefin was not obtained.

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.09; H, 9.15. Found: C, 69.03; H, 9.16.

However, addition of chlorine followed by hydrolysis and treatment with *p*-nitrophenylhydrazine gave an osazone, m.p. 235–237°. The known *p*-nitrophenylosazone of 1,2-cyclohexanedione is 236–237°.[15] This derivative indicates the presence of a major quantity of 2-methyl-5,6,7,8-tetrahydro-1,4-benzodioxane in the olefin fraction. A similar series of experiments on the condensation products of cyclohexene oxide with ethylene glycol produced only an impure sample of what was believed to be a lactone. No product corresponding to a dioxene was found.

Abnormal Dehydrogenation of 4-Oxaheptane-1,6-diol.—The diol was prepared in 36% yield by alkaline condensation of propylene oxide with an excess of 1,3-propanediol. When a slurry of 67 g. (0.5 mole) of the crude diol with 4 g. (6%) of the catalyst was heated, hydrogen was evolved. The liquid distillation products on refractionation gave 14 g., b.p. 50–54°, and 10.5 g., b.p. 146–150°. The lower boiling fraction was identified as propanal by the formation of the *p*-nitrophenylhydrazone, m.p. 123–124° (lit. m.p. 125°), and of the 2,4-dinitrophenylhydrazone, m.p. 153° (lit. m.p. 154°).[16] The higher boiling fraction was identified as acetol by the formation of the phenylosazone, m.p. 149–150° (lit.,[17] 150°). Spectra of both samples were consistent with these assignments, with the qualification that the propanal contained an unsaturated impurity.

Preparation of Butyrolactone.—A slurry of 90 g. (1 mole) of 1,4-butanediol and 4.5 g. (5%) of catalyst was heated to evolution of hydrogen and distillation of product, *ca.* 200°. On redistillation, 79 g. of butyrolactone, b.p. 204–205°, resulted for a yield of 92%.

Polymer from 1,6-Hexanediol.—The catalyst, 3.5 g., was suspended in 118 g. (1 mole) of melted 1,6-hexanediol and the mixture heated gradually. Hydrogen was evolved and liquid products distilled normally at about 130°. After about 50 ml. of liquid had been collected, the reaction became exothermic, the rate of gas evolution increased markedly and a black, spongy material, not unlike foam rubber, filled the flask, distilling column, and condensers. The liquid contained several components, one of which was identified as 2-methylcyclopentanone by the formation of a semicarbazone, m.p. 181°, after sublimation (lit.,[18] m.p. 182°).

Acknowledgment.—We wish to thank Dr. James G. Traynham for discussions and the loan of facilities during the preparation of this manuscript.

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Decarboxylation and Deuterium Exchange in Some Azabicyclic Ketone Systems[1]

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Studies of the decarboxylation of the keto acid **2** (to form **1b**) and of deuterium exchange with the bicyclic amino ketones **1** (to form **3**) indicate that both of these reactions proceed *via* monocyclic intermediates.

Studies of the synthesis of the azabicyclic ketones **1**[2,3] had shown that boiling 20% hydrochloric acid would effect the hydrolysis and decarboxylation of the ester, **2**, to produce **1b** in 60–70% yield. We have found that this same reaction, utilizing 20% deuterium chloride in deuterium oxide, forms the dideuterio ketone, **3b**. However, application of the same reaction conditions to the keto acid, **4**, previously reported[4] to be thermally stable, resulted in no reaction and application of this decarboxylation precedure to the diester, **5**, resulted in the formation of the diacid, **6a**, characterized as its ester, **6b**. It is also pertinent to note that compounds **7**[5] and **8**[6] have been found stable to thermal decarboxylation, whereas compounds containing the systems **9**[7,8] and **10**[9,10] have been decarboxylated successfully at temperatures above

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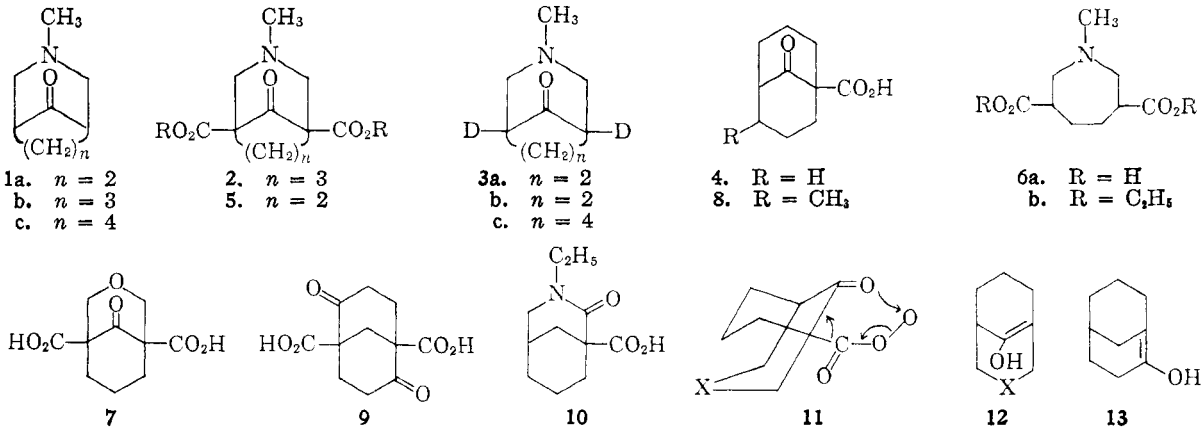


1a. $n = 2$ b. $n = 3$ c. $n = 4$ 2. $n = 3$ 5. $n = 2$ 3a. $n = 2$ b. $n = 2$ c. $n = 4$ 4. R = H 8. R = CH_3 6a. R = H b. R = C_2H_5

7 9 10 11 12 13

200°. The majority of these results are not inconsistent with the usual cyclic mechanism (as in **11** → **12**) for decarboxylation if one considers that the bicyclo[3.3.1]nonane system represents a borderline case for existence of compounds with a bridgehead double bond.[11,12] For such borderline cases, seemingly minor differences in structure may well be sufficient to cause the strain of a bridgehead double bond to be prohibitive in one case (as in **12**) but not in another (as in **13**). The intuitive expectation that enol **12** should be appreciably more strained than enol **13** is readily verified by measuring with Dreiding Molecular Models the distances which separate atoms prior to forming the last bond in these two systems. As noted elsewhere,[10] changes in the geometry of the system **10** may well influence the relative ease of decarboxylation with compounds which contain the same bicyclic system. From these considerations, one would conclude that while structures **9** and **10** can decarboxylate (*via* the enol, **13**), structures **2**, **4**, **7** and **8** should all be substantially more stable if their decarboxylation requires formation of the enol, **12**. Since the decarboxylation of the keto acid, **2** (R = H), occurs at much lower temperatures than any of the other compounds discussed, the suggested[2] normal decarboxylation path (*via* **11**) is clearly incorrect.

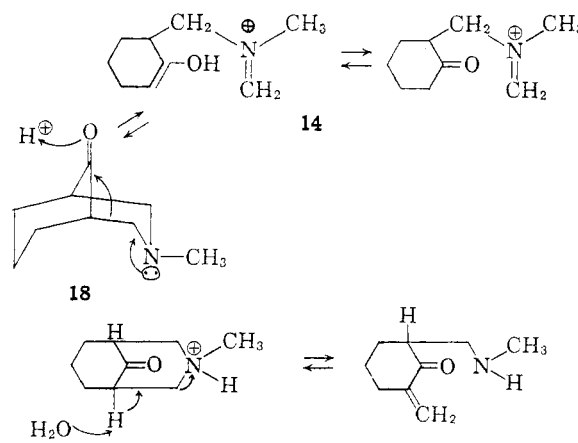
In an effort to determine the relative ease of forming bridgehead enols from the azabicyclic ketones **1**, each of these materials was heated with 20% deuterium chloride in deuterium oxide. The results (Table I) of these hydrogen–deuterium exchange experiments to form the dideuterio ketones, **3** (see Experimental), are striking in two respects. First, relative rates at which the ketones **1** incorporate deuterium (**1a** > **1b** > **1c**) increase with increasing strain in the molecules. In addition, the usual statistical deuterium distribution is not obtained, since essentially all of the deuterated

TABLE I

DEUTERIUM EXCHANGE EXPERIMENTS WITH THE AMINO KETONES, 1

Compound	Reaction time, days	Recovery, %	Deuterium distribution, % d_0	d_1	d_2
1a	12	92	40	6	54
1b	14	94	55	4	41
1b	3	81	75	3	22
1c	4	96	90	2	8

compounds contain two deuterium atoms per molecule. These results are definitely incompatible with incorporation of deuterium *via* a bicyclic enol (*e.g.* **12**, X=NCH_3) and indicate that deuterium is being incorporated into a monocyclic intermediate which recloses to the bicyclic ketones, **1**. Of the various monocyclic intermediates which might be envisioned, we believe that only two, **14** and **15**, deserve consideration. Of these two intermediates structure **14** is much more reasonable, since it represents the intermediate in the intramolecular Mannich reaction[13] which was employed to form[3] the azabicyclic ketones, **1**. Since the deuterium exchange reactions were essentially free from by-products, we conclude that the cyclization of the intermediate, **14**, is a particularly clean



14 18 15

(10) J. P. Ferris and N. C. Miller, 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., September 9–14, 1962, Abstracts of papers, p. 47Q.

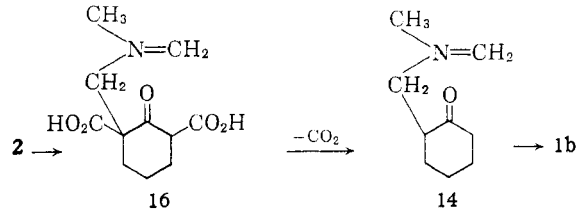
(11) F. S. Fawcett, *Chem. Rev.*, **47**, 219 (1950).

(12) Bicyclo[4.2.1]nonan-9-one, a compound with the same S = 7 (ref. 11), has been found to exchange its α-hydrogen atoms for deuterium very slowly. K. Biemann, unpublished work.

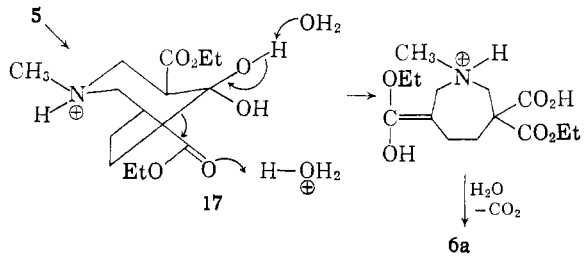
(13) (a) F. F. Blicke, *Org. Reactions*, **1**, 303 (1942); (b) H. Hellmann and G. Opitz, *Angew. Chem.*, **68**, 265 (1956); (c) B. Reichert "Die Mannich-Reaktion," Springer Verlag, Berlin, 1959.

reaction in the absence of other acceptors for the Mannich intermediate and hope to utilize this idea to improve the syntheses[3] of the bicyclic ketones, **1**.[14]

From these considerations, the most probable course of the decarboxylation of the keto acid, **2**, (R = H), is that shown in the accompanying equation where decarboxylation occurs after formation of the monocyclic intermediate, **16**. The differing



behavior of the ester, **5** (R = Et), which forms the diacid, **6a**, under comparable reaction conditions, is perhaps best attributed to the formation of a very stable ammonium salt hydrate, **17**, analogous to the products obtained with salts of **1a**.[3] The fact that the bicycloöctane system, **1a**, is also the strongest base of the series is also in accord with this idea since reversal of the Mannich reaction (as in **18**) requires the unprotonated amine. The process indicated with arrows in **17** provides a possible course for the formation of **6a**.

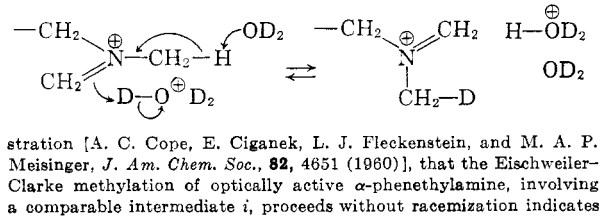


Of incidental interest was the finding that the double carbonyl stretching frequency observed in the spectra of the bicyclic amino ketones, **1**,[15] is substantially modified (see Experimental) in the dideuterio ketone, **3b**. This result provides compelling evidence that the carbonyl doublets in such compounds are attributable to Fermi resonance between the carbonyl stretching vibration and one of the bending vibrations (see Experimental) of an adjacent C—H or C—C bond.[16]

Experimental[17]

Decarboxylation of 1,5-Dicarboethoxybicyclo[3.3.1]-3-azanonan-9-one (2, R = C_2H_5).—The diester, **2**, prepared as previously described,[2] was obtained as a colorless liquid, b.p. 139–144° (0.22–0.35 mm.), $n^{25}D$ 1.4822 [lit.,[2] 157–159° (0.15 mm.)] with infrared absorption[18] at 1730 cm.$^{-1}$ (broad, ester and ketone C=O), end absorption (ϵ 860 at 220 mμ) in the ultraviolet[19] and n.m.r. absorption[20] at 5.78 τ (4H, quadruplet with J = 7 c.p.s., ethoxyl CH_2), at 6.89 τ (4H, singlet, CH_2—N), at 7.65 τ (3H, singlet, CH_3N) and at 8.72 τ (6H, triplet with J = 7 c.p.s., ethoxyl CH_3). After a solution of 24 g. (0.081 mole) of the diester, **2**, in 125 ml. of 20% aqueous hydrochloric acid had been refluxed for 24 hr., the reaction mixture was extracted with chloroform, made basic with sodium hydroxide, and extracted with chloroform. The chloroform extract was dried, concentrated, and distilled to separate 8.24 g. (66.5%) of the ketone **1b**, b.p. 86° (5 mm.), $n^{24}D$ 1.4901, identified with the previously described[3] sample by comparison of infrared spectra and by conversion in 78% yield to the previously described[3] *p*-toluenesulfonic acid salt, m.p. 182–184°. Repetition of this reaction employing 1.0 g. (3.4 mmoles) of the diester, **2**, and 5 ml. of a 20% solution of deuterium chloride in deuterium oxide[21] afforded 320 mg. (62%) of the deuterio ketone, **3b**, b.p. 85° (5 mm.), which was further purified by conversion to the *p*-toluenesulfonic acid salt, m.p. 182–183°, in 78% yield and reconversion to the ketone **3b**, b.p. 90° (6 mm.). Mass spectrometric analysis indicated that the ketone contained 2% d_1 species, 95% d_2 species, and 3% of d_3 and more highly deuterated species. The infrared spectrum[18] of the ketone **3b** has a weak band at 2180 cm.$^{-1}$ (C—D) and two C=O stretching bands at 1715 (strong) and 1756 (weak) cm.$^{-1}$ in the 6-μ region rather than the bands at 1730 (strong) and 1710 (weak) cm.$^{-1}$ found in the spectrum of **1b**. In addition, the spectrum of **3b** has a band at 910 cm.$^{-1}$, lacking in the spectrum of **b,1** and lacks absorption at 850 cm.$^{-1}$ where the spectrum of **1b** has a band. It is presumably the overtones of these bands at 850 and 910 cm.$^{-1}$ which couple with the fundamental carboxyl stretching frequency to produce the observed doublets. The spectra of **1b** and **3b** also differ in a number of other

(14) The failure to observe the incorporation of additional deuterium *via* the equilibration illustrated in the accompaning equation might be considered to exclude the intermediate, **14**. However, the demonstration [A. C. Cope, E. Ciganek, L. J. Fleckenstein, and M. A. P. Meisinger, *J. Am. Chem. Soc.*, **82**, 4651 (1960)], that the Eischweiler–Clarke methylation of optically active α-phenethylamine, involving a comparable intermediate *i*, proceeds without racemization indicates



that in acid solution the aforementioned equilibration must occur very slowly, if at all.

(15) The same phenomenon has been observed with certain of the analogous carbocyclic ketones. See C. S. Foote, Ph.D. dissertation, Harvard University, 1961.

(16) See (a) R. N. Jones, C. L. Angell, T. Ito, and R. J. D. Smith, *Can. J. Chem.*, **37**, 2007 (1959); (b) P. Yates and L. L. Williams, *J. Am. Chem. Soc.*, **80**, 5896 (1958).

(17) All melting points are corrected and all boiling points are uncorrected. Unless otherwise stated, magnesium sulfate was employed as a drying agent. The infrared spectra were determined with either a Baird, Model B, or a Perkin–Elmer Model 21, infrared recording spectrophotometer fitted with a sodium chloride prism. The ultraviolet spectra were determined with a Cary recording spectrophotometer, Model 14. The n.m.r. spectra were determined at 60 Mc. with a Varian, Model A-60, n.m.r. spectrometer. The mass spectra were obtained with a CEC, Model 21–130, mass spectrometer. The microanalyses were performed by Dr. S. M. Nagy and his associates and by the Scandinavian Microanalytical Laboratory.

(18) Determined in carbon tetrachloride solution.

(19) Determined in heptane solution.

(20) Determined as a solution in deuteriochloroform.

(21) This solution was prepared by reaction of freshly distilled phosphorus trichloride with deuterium oxide followed by distillation.

places in the fingerprint region. The n.m.r. spectrum[22] of the *p*-toluenesulfonic acid salt of **3b** resembles the previously reported[3] spectrum of the *p*-toluenesulfonic acid salt of **1b** with a quadruplet (J = 13 c.p.s.) centered at 6.33 τ (4H, $CH_2N^{\oplus}$—), a singlet at 7.03 τ (3H, $CH_3N^{\oplus}$—), and a singlet at 7.62 τ (3H, aryl CH_3). This spectrum of the salt of **3b** differs from the spectrum of the salt of **1b** in the presence of a less complex pattern (typical AB pattern for the salt of **3b**) for the peak centered at 6.33 τ and the absence of complex absorption in the region 7.5 to 7.9 τ attributable to the bridgehead protons.

Preparation and Hydrolysis of 1,5-Dicarboethoxybicyclo[3.2.1]-3-azaoctan-8-one (5, R = C_2H_5).—A sample of the diester, **5**, prepared as previously described,[23] was found both by thin layer chromatography and examination of its n.m.r. spectrum to contain two components, the lesser component (probably the monoester) comprising about 30% of the mixture. Reaction of 4.86 g. (17.2 mmoles) of this mixture with 3.27 g. (17.2 mmoles) of *p*-toluenesulfonic acid monohydrate in 20 ml. of acetone followed by recrystallization from acetone yielded 3.94 g. (48%) of the monohydrate (see structure **17**) of the *p*-toluenesulfonic acid salt of **5** (R = C_2H_5) as white plates, m.p. 138.5–140°. The material has infrared absorption[24] at 3490 cm.$^{-1}$ (assoc. OH) and at 3270 cm.$^{-1}$ (assoc. N—H) with only weak absorption at 1725 cm.$^{-1}$ (C=O) and an ultraviolet maximum[25] at 222 mμ (ϵ 10,800) as well as a series of weak maxima (ϵ 291 at 263 mμ) in the region 250–270 mμ.

Anal. Calcd. for $C_{21}H_{31}NO_9S$: C, 53.26; H, 6.60; N, 2.96. Found: C, 53.05; H, 6.65; N, 2.94.

A 2.035-g. (4.3 mmoles) sample of this salt was reconverted to the free base, **5** (R = C_2H_5), by the previously described[3] procedure. The pure free base, a colorless oil b.p. 135° (0.25 mm.), has infrared absorption at 1763 cm.$^{-1}$ (cyclopentanone C=O) and at 1730 cm.$^{-1}$ (ester C=O) with only end absorption (ϵ 680 at 220 mμ) in the ultraviolet[19] and n.m.r. absorption[20] at 5.77 τ (4H, quadruplet with J = 7 c.p.s., ethoxyl CH_2) as well as a quadruplet (J = 11 c.p.s.) centered at 7.07 τ (4H, CH_2—N<), a singlet at 7.56 τ (CH_3—N), and a triplet (J = 7 c.p.s.) centered at 8.73 τ (6H, ethoxyl CH_3).

A solution of 1.00 g. (3.5 mmoles) of the diester, **5** (R = C_2H_5), in 5 ml. of 20% aqueous hydrochloric acid was refluxed for 15 hr. and then extracted with ether and the aqueous phase was concentrated.[26] The white solid residue (927 mg. of crude **6a**, m.p. 188–195° dec.) was dissolved in 30 ml. of ethanol and the solution was saturated with dry hydrogen chloride and allowed to stand at room temperature for 3 days. The resulting solution was concentrated, made basic with cold aqueous potassium carbonate, and extracted with ether. The ethereal extract was dried, concentrated, and distilled in a short-path still (130° at 0.1 mm.) to separate 700 mg. (88%) of the diester **6b**, $n^{24}D$ 1.4630, with infrared absorption[18] at 1732 cm.$^{-1}$ (ester C=O), an ultraviolet maximum[25] at 290 mμ (ϵ 65), and n.m.r. absorption[20] at 5.88 τ (4H, quadruplet with J = 7 c.p.s., ethoxy CH_2) as well as a singlet at 7.22 τ (CH_2—N) superimposed on more complex absorption (—CH<) corresponding to a total of six protons, a singlet at 7.58 τ (3H, CH_3N<), a broad peak centered at 8.07 τ (4H, CH_2CH_2), and a triplet (J = 7 c.p.s.) centered at 8.78 τ (6H, ethoxyl CH_3).

Anal. Calcd. for $C_{13}H_{23}NO_4$: C, 60.68; H, 9.01; N, 5.44; mol. wt., 257. Found: C, 60.89; H, 8.91; N, 5.42; mol. wt., 257 (mass spectrum).

Stability of the Keto Acid 4.—A mixture of 182 mg. (1 mmole) of the keto acid and 10 ml. of 19% aqueous hydrochloric acid was refluxed for 3 days and then extracted with ether. The ethereal solution was extracted with aqueous sodium bicarbonate and the acid, recovered from the bicarbonate solution in the usual way, amounted to 179 mg. (98.3%) of the starting material, m.p. 132–135°. Recrystallization from an ether–petroleum ether mixture afforded 155 mg. (85%) of the pure keto acid, m.p. 137–138°, which did not depress the melting point of the starting material.

Deuterium Exchange Experiments.—Solutions of the amino ketones, **1**, in 20% deuterium chloride in deuterium oxide were heated to 100° in sealed ampoules for the time specified in Table I. The resulting mixtures were extracted with ether, made basic with aqueous sodium hydroxide, and again extracted with ether. After the ethereal solutions had been dried and concentrated, distillation of the residues afforded the amino ketones **1** and **3** in the yields specified in Table I. The materials were converted to their previously described[3] *p*-toluenesulfonic acid salts and then reconverted to the amino ketones **1** and **3** for mass spectrometric analysis. The n.m.r. spectra of the *p*-toluenesulfonic acid salts of the products derived from both **1a** and **1b** were consistent with the location of the deuterium as indicated in **3a** and **3b** as previously discussed, the salt of **1a** + **3a** having absorption of diminished intensity in the region 7.5–7.9 τ (bridgehead C—H). No rigorous conclusion could be drawn from such data for the material derived from the ketone **1c** because of the low deuterium content.

(22) Determined in a solution of 20% deuterium chloride in deuterium oxide.

(23) E. F. L. J. Anet, G. K. Hughes, D. Marmion, and E. Ritchie, *Australian J. Sci. Res.*, **3A**, 330 (1950).

(24) Determined as a Nujol mull.

(25) Determined as a solution in 95% ethanol.

(26) Earlier experiments had established that no material could be recovered by making the aqueous extract basic and extracting with organic solvents.