triturated with ice–water. The suspended solid was collected by filtration and purified by vacuum sublimation to give 1.7 g. (39%) of colorless crystals, m.p. 216–218°.

Anal. Calcd. for $C_7H_9N_2O_2Cl$: C, 44.57; H, 4.81; N, 14.85. Found: C, 44.80; H, 4.86; N, 14.99.

2-Phenyl-4-hydroxy-5-chloro-6-ethoxypyrimidine (XII).—An ethanolic solution of 5.5 g. of ethyl α-chloro-β,β-diethoxyacrylate and benzamidine (prepared by treatment of an ethanolic solution of 7.8 g. of benzamidine hydrochloride with the calculated amount of sodium ethoxide) was heated under reflux for 3 hr., evaporated to approximately 50 ml. under reduced pressure and poured into ice-cold diluted hydrochloric acid. The precipitate which separated was collected by filtration, dried, and purified by vacuum sublimation; yield, 1.0 g. (16%), m.p. 274°.

Anal. Calcd. for $C_{12}H_{11}N_2O_2Cl$: C, 57.49; H, 4.43; N, 11.17. Found: C, 57.26; H, 4.38, N, 10.99.

2,4-Diamino-5-chloro-6-ethoxypyrimidine (XV). Method A.—A mixture of 1.6 g. of α,β,β-trichloroacrylonitrile, 1.8 g. of guanidine carbonate, and 3.4 g. of sodium ethoxide in 75 ml. of ethanol was heated under reflux for 5 hr. and then poured into 50 ml. of ice water. The solid which separated was collected by filtration, dried. and sublimed *in vacuo* to give 1.2 g. (62%), m.p. 132°.

Anal. Calcd. for $C_6H_9N_4OCl$: C, 38.20; H, 4.81; N, 29.71; Cl, 18.80. Found: C, 38.29; H, 4.87; N, 29.82; Cl, 18.89.

Method B.—A mixture of 1.5 g. of guanidine and 2.6 g. of the imino ether of α-chloro-β,β-diethoxyacrylonitrile in 20 ml. of dimethylformamide was heated at 100° for 45 min. and then evaporated to near dryness under reduced pressure. The residue was poured into water and the precipitated solid purified as described above to give 2.2 g. (99%), m.p. 132°.

2,4-Diamino-5-chloro-6-hydroxypyrimidine (XVIII).—A mixture of 2.0 g. of 2,4-diamino-5-chloro-6-ethoxypyrimidine and 25 ml. of concentrated hydrochloric acid was heated under reflux. A white solid started to precipitate from the reaction mixture after 5 min. After 30 min. of heating, the solid was collected by filtration, washed well with water, and recrystallized from water to give 1.2 g. (64%), m.p. 338–341°. A final purification for analysis was made by vacuum sublimation at 280°; m.p. 341–342°.

Anal. Calcd. for $C_4H_3N_4OCl$: C, 29.92; H, 3.14. Found: C, 30.36; H, 3.07.

2-Methyl-4-amino-5-chloro-6-ethoxypyrimidine (XVI). Method A.—A mixture of 5.2 g. of α,β,β-trichloroacrylonitrile and acetamidine (prepared from 12.6 g. of acetamidine hydrochloride and the calculated amount of sodium ethoxide) in 100 ml. of ethanol was stirred at room temperature for 30 min. and then poured into 150 ml. of water. The precipitated solid was collected by filtration, dried, sublimed *in vacuo*, and then recrystallized from methanol to give 2.5 g. (40%), m.p. 161°.

Anal. Calcd. for $C_7H_{10}N_3OCl$: C, 44.81; H, 5.37; N, 22.40. Found: C, 45.17; H, 5.44; N, 21.96.

Method B.—A mixture of 3.7 g. of the imino ether of α-chloro-β,β-diethoxyacrylonitrile, 7.8 g. of acetamidine hydrochloride, 40 ml. of ethanol, and 40 ml. of 2 *N* sodium ethoxide in ethanol was evaporated under reduced pressure until all the ethanol had been removed, and the residue was then heated for 45 min. by means of an oil bath maintained at 100°. Addition of 20 ml. of ice–water to the residue precipitated a solid which was collected by filtration, washed thoroughly with water, dried, and sublimed *in vacuo* to give 3.0 g. (96%), m.p. 161°.

2-Phenyl-4-amino-5-chloro-6-ethoxypyrimidine (XVII).—A mixture of 3.3 g. of the imino ether of α-chloro-β,β-diethoxyacrylonitrile and 2.4 g. of benzamidine in 15 ml. of ethanol was evaporated to dryness under reduced pressure and the residue heated in an oil bath maintained at 100°. After 20 min. the reaction mixture was triturated with 50 ml. of ice–water. The oil which initially separated soon solidified and was collected by filtration and recrystallized from aqueous methanol to give 3.5 g. (94%), m.p. 91.5–92°.

Anal. Calcd. for $C_{12}H_{12}N_3OCl$: C, 57.72; H, 4.85; N, 16.83. Found: C, 57.14; H, 4.70; N, 16.47.

N-Arylazetidines

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Two possible routes to N-arylazetidines have been examined. N-Phenylazetidine and N-*p*-tolylazetidine may be prepared by cyclization of the corresponding N-(3-bromopropyl)arylamines, a reaction which appears to be inhibited by electron-withdrawing substituents. N-Arylazetidines containing *ortho* or *para* nitro groups may readily be prepared by reaction of azetidine with the corresponding haloaromatic compound.

Azetidine is the least accessible of the lower alkylenimines, and many of its simpler derivatives are still unknown. Of the N-substituted azetidines, most of the known N-alkyl compounds are obtained in low yield, particularly when the alkyl group is small, and when this work began no N-aryl derivative had been prepared. An early claim to the preparation of N-phenylazetidine had been discounted[1] and, as a study consequent upon this work, we examined the possibility of preparing compounds of this series.

Of the possible preparative approaches to N-arylazetidines, we have examined two. The first involves the cyclization of intermediates of the type $ArNH(CH_2)_3X$. This particular method has been used in the synthesis of N-alkyl compounds, examples being the base-catalyzed cyclization of compounds in which X is a halogen atom[2,3] or a hydrogen sulfate group.[4] The second approach to N-arylazetidines involves nucleophilic substitution by azetidine on a suitably substituted benzene ring.

Cyclization.—N-(3-Bromopropyl)aniline was prepared through the corresponding alcohol. The action of hot (100°) 50% sodium hydroxide solution on the hydrobromide salt afforded small amounts of two products identified as 1,2,3,4-tetrahydroquinoline and julolidine (2,3,6,7-tetrahydro-1H,5H-benzo[*ij*]quinolizine). This result was in contrast to that obtained for the salt $MeNHCH_2CMe_2Br \cdot HBr$, which under similar conditions was known to yield the N-methylazetidine derivative.[3] The present result is apparently to be attributed to solubility difficulties; it is likely that the hydroxide had not, in fact, reacted with the bromopropylaniline, because on dry distillation of the base, the same products, tetrahydroquinoline and julolidine, could be obtained. When use was made of aqueous ethanolic sodium hydroxide, in which solubility troubles were absent, the major product was the substitution

(1) A. Fischer, R. D. Topsom, and J. Vaughan, *J. Org. Chem.*, **25**, 463 (1960).

(2) (a) M. Kohn, *Ann.*, **351**, 134 (1907); (b) M. Kohn, *Monatsh.*, **28**, 423 (1907); (c) M. Kohn and J. Giaconi, *ibid.*, **28**, 461 (1907); (d) M. Kohn and D. Morgenstern, *ibid.*, **28**, 479, 529 (1907).

(3) C. Mannich and G. Baumgarten, *Ber.*, **70**, 210 (1937).

(4) (a) W. R. Vaughan, R. S. Klonowski, R. S. McFlhinney, and B. B. Millward, *J. Org. Chem.*, **26**, 138 (1961); (b) S. Searles, M. Tamres, F. Block, and L. A. Quarterman, *J. Am. Chem. Soc.*, **78**, 4917 (1956); (c) A. T. Bottini and J. D. Roberts, *ibid.*, **80**, 5203 (1958); (d) R. C. Elderfield and H. A. Hageman, *J. Org. Chem.*, **14**, 623 (1949).

product, N-(3-ethoxypropyl)aniline. In this case, however, a small yield of N-phenylazetidine (7–8%) was obtained, together with some of the elimination product, N-allylaniline. Conditions similar to these were used by Heine, *et al.*, for the preparation of the related N-phenylaziridine.[5,6]

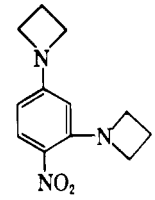
When the cyclizing agent was *t*-butoxide, and reaction was carried out in *t*-butyl alcohol the main product was N-allylaniline and no evidence was obtained for N-phenylazetidine formation. This change in reaction from substitution to elimination, is in line with increased basicity of cyclizing agent. It may also be noted that any ethanol impurity in the *t*-butyl alcohol was found to lead to ethoxypropylaniline formation.

Cyclization was also attempted with two compounds related to N-(3-bromopropyl)aniline, namely the *p*-methyl and *p*-chloro derivatives. On reaction with ethanolic hydroxide, the major product in each case was the expected ether, while the ratio of N-arylazetidine to N-allylarylamine varied considerably. The *p*-methyl compound gave rise to the azetidine in 9% yield, almost free from accompanying N-allylamine. From the *p*-chloro compound, the assumed azetidine was obtained only in trace yield; separation from the large amount of accompanying N-allyl product was possible only by gas chromatography. The trend in product composition would indicate that with electron-withdrawing substituents, azetidine preparation by these means is likely to be impracticable.

Nucleophilic Substitution.—If, in a closely related alkylenimine series, the order of nucleophilicity follows the order of basicity, then azetidine should be a stronger nucleophile than is piperidine. It should therefore react with activated halobenzenes to yield N-arylazetidines, provided that the activating substituent itself does not react with azetidine, and that excess azetidine (or other base) is present to prevent fission of the azetidine by the released hydrogen halide.

The azetidine for use in this work was prepared by the reduction of *p*-toluenesulphonazetidide with sodium and amyl alcohol. With one difference, the method followed was that of Vaughan, *et al.*,[4a] who assumed that the amine layer, separating out in the final stage of the procedure, was azetidine. We obtained an amine layer of corresponding bulk but which was always, at this stage, a mixture of amines. This layer was distilled to yield approximately equal parts of azetidine and a higher boiling amine which was identified as octahydrodiazocine. Our azetidine yields were thus substantially lower than that reported by Vaughan, *et al.*

Several bromoaromatic and two chloroaromatic compounds were allowed to react with excess azetidine. Those halo compounds, from which azetidyl derivatives were isolated, contained *ortho* or *para* nitro substituents, although groups other than halogen were sometimes displaced. Thus *o*-nitro-, *p*-nitro-, and 3-methyl-4-nitrobromobenzenes gave the expected N-arylazetidines, as did *p*-chloronitrobenzene and 1-chloro-2,4-dinitronaphthalene. 3,4-Dinitro- and 3-methoxy-4-nitrobromobenzene each gave the same product, *viz.* 2,4-bis(N,N′-azetidino)nitrobenzene.



Yields obtained at 50° ranged from 40%, for *o*-bromonitrobenzene after 10 days, to 95% for *p*-bromonitrobenzene after two days. All the above haloaromatics appeared to react cleanly to give products readily isolated and purified.

Other haloaromatics, containing neither *ortho* nor *para* nitro substituents, did not react in this way. Bromobenzene, 2-bromonaphthalene, and *p*-bromochlorobenzene were all recovered unchanged from their respective reaction mixtures after several weeks at 50°. *m*-Bromonitrobenzene and 3,5-dinitrobromobenzene gave immediate, very intense colors and in each case the reaction yielded a dark unidentified pitch. Similar difficulties have been encountered in other work involving reaction of piperidine with halobenzenes carrying *meta* nitro groups. The white, tacky product from *p*-bromobenzonitrile was equally intractable although its physical appearance indicated a completely different reaction course from that followed by the *m*-nitro compounds.

Experimental

All melting and boiling points are uncorrected. Analyses were by the Microanalytical Laboratory of the University of Otago. Infrared spectra were recorded on a Perkin–Elmer Model 221 instrument. The spectra of the azetidines made were compared with spectra of similar N-arylpiperidines and pyrrolidines and with N-alkylazetidines prepared for this purpose. They showed no unexpected features. Gas chromatographic separations were performed with a Beckman "Megachrom" using columns packed with 35% Apiezon J on C22 firebrick and a column temperature of 180°.

N-(3-Bromopropyl)anilinium Bromide (I).—To redistilled aniline (103 g.) at 55° was added, dropwise and with stirring, 3-bromopropan-1-ol (25 g.), and the mixture was kept at 55° for 1.5 hr. The solution gradually turned dark red and anilinium bromide crystallized out of solution. The cooled solution, made slightly alkaline with dilute sodium hydroxide solution, was extracted with ether (300 ml.), and the ether extract was well washed with water before drying ($MgSO_4$). Ether was removed and aniline was distilled at 11 mm., at which pressure the 3-hydroxypropylaniline was collected (24 g., 88.5%; b.p. 172–179°/11 mm.). To 20 g. of the hydroxyamine, hydrobromic acid (60 ml., s.g. 1.48) was gradually added after both reactants had been cooled below 0°. After 1.5 hr., constant-boiling hydrobromic acid was removed by distillation and the residue was cooled. I crystallized (2 hr.) and was recrystallized from ethanol, followed by (20:80) ethanol–benzene. The yield was 25 g. (64%) and the m.p. was 131–132°.

Anal. Calcd. for $C_9H_{13}Br_2N$: C, 36.61; H, 4.41; N, 4.76. Found: C, 36.82; H, 4.63; N, 4.75.

A small sample of the hydrobromide was neutralized with dilute sodium hydroxide solution, and the mixture was extracted with ether. Removal of ether left a sample of N-(3-bromopropyl) aniline, an unstable oil tending to decompose above room temperature.

Anal. Calcd. for $C_9H_{12}BrN$: Br, 37.38. Found: Br, 37.10.

N-(3-Bromopropyl)-*p*-toluidinium Bromide (II).—This was prepared in a manner similar to that of I, in 33% yield; m.p. 151° after recrystallization from ethanol.

Anal. Calcd. for $C_{10}H_{15}Br_2N$: C, 38.83; H, 4.85; Br, 51.78. Found: C, 38.63; H, 4.65; Br, 51.80.

N-(3-Bromopropyl)-*p*-chloroanilinium Bromide (III).—3-Bromopropan-1-ol (75 g.) was added, dropwise and with stirring, to redistilled *p*-chloroaniline (125 g.; b.p. 120°/13 mm.). The

(5) H. W. Heine, B. L. Kapur, and C. S. Mitch, *J. Am. Chem. Soc.*, **76**, 1173 (1954).

(6) A. T. Bottini [*ibid.*, **84**, 734 (1962)] has recently reported the preparation of N-phenylazetidine in 8% yield by following Heine's conditions. This report reached us after submission of our paper.

temperature was kept at 80° to prevent solidification of the reaction mixture; otherwise the preparation followed that of I. III was recrystallized from ethanol and 110 g. was obtained, (62%) melting at 175–176°.

Anal. Calcd. for $C_9H_{12}Br_2ClN$: C, 32.78; H, 3.64; N, 4.25; halogen, 59.33. Found: C, 33.17; H, 3.63; N, 3.96; halogen, 59.2.

Reaction of I with Base. A. With Sodium Hydroxide.—I (25 g.) was added to sodium hydroxide (12.5 g.) in water (25 ml.) and the mixture was heated to 100°. A red oil formed and the viscosity appeared to increase as the reaction proceeded. After 45 min., ethanol (25 ml.) was added and the mixture was heated for a further 30 min. The viscous red oil did not dissolve. Ethanol was distilled (pump) and the residue was extracted with ether (100 ml.). The well washed ether layer was dried over sodium carbonate, the ether was distilled, and the red oily residue was distilled at 23 mm. Some breakdown occurred during distillation, but small 1,2,3,4-tetrahydroquinoline and julolidine fractions were obtained. The infrared spectrum of the tetrahydroquinoline ($n^{25}D$ 1.5929) was identical with that of an authentic sample; the julolidine was identified by a mixed melting point of the hydrobromide with that of an authentic specimen.

B. With Potassium *t*-Butoxide.—*t*-Butyl alcohol was freed from ethanol by treatment with potassium dichromate and by subsequent fractionation. Potassium (6.63 g.) was dissolved in *t*-butyl alcohol (250 ml.) and I (24 g.) was added slowly and with stirring, the temperature being kept at 50–55°. Potassium bromide was precipitated and the solution became orange. After addition was complete, the temperature was raised to 85–90° for 1 hr. Heating was discontinued and after an additional 2 hr. the solution was filtered free from potassium bromide and washed with ether. Ether and *t*-butyl alcohol were removed under reduced pressure and the residue was distilled using a Vigreux column at 1 mm. Two main fractions were collected, a yellow fraction (3.8 g.) at 72–78°, and a colorless fraction (3.2 g.) turning orange on standing, at 125–145°. The lower boiling liquid was refractionated to yield a pure sample of N-allylaniline, b.p. 72–74°/1 mm., $n^{20}D$ 1.5645, infrared spectrum identical with that of a known sample. The higher boiling main fraction could not be resolved into simple components. When the whole experiment was first run, untreated *t*-butyl alcohol was used and a fraction, b.p. 158–162°/24 mm., was obtained. The liquid had $n^{27}D$ 1.5320 and the infrared spectrum showed an acyclic ether peak at 9 μ. The boiling point, refractive index, and spectrum indicated N-(3-ethoxypropyl)aniline.

Anal. Calcd. for $C_{11}H_{17}NO$: C, 73.74; H, 9.50; N, 7.82. Found: C, 74.11; H, 9.70; N, 7.72.

C. With Aqueous Ethanolic Sodium Hydroxide.—I (24 g.) was dissolved in water (35 ml.)–96% ethanol (40 ml.) and added to a mixture of sodium hydroxide solution (32 ml., 6 *N*) and 96% ethanol (80 ml.). The temperature was kept at 50° during the addition, and then raised to 85° for an additional hour. Ethanol (90 ml.) was distilled and the residue, after cooling, was extracted (3 × 100 ml.) with ether. The ether extracts were washed and dried (magnesium sulfate), ether and ethanol were distilled from the solution, and the remaining liquid was distilled through a Vigreux column at 11 mm. to yield two main fractions; one was collected at 104–112° (1.1 g.) and the other was collected at 130–150° (3.7 g.). The first fraction proved, on gas chromatography, to be a 2:1 mixture of N-phenylazetidine and N-allylaniline. The azetidine was a colorless liquid, $n^{23.5}D$ 1.5695; its infrared spectrum was compatible with the assumed structure.

Anal. Calcd. for $C_9H_{11}N$: C, 81.2; H, 8.27; N, 10.53. Found: C, 80.93; H, 8.35; N, 10.80.

The azetidine picrate formed in ethanol as yellow needles, m.p. 110°.

Anal. Calcd. for $C_{15}H_{14}N_4O_7$: C, 49.72; H, 3.87; N, 15.47. Found: C, 49.83; H, 4.26; N, 15.40.

The second fraction proved on redistillation to be mainly N-(3-ethoxypropyl)aniline, b.p. 142–144°/11 mm., $n^{22.5}D$ 1.5338. Its infrared spectrum showed the characteristic ether peak at 9 μ.

Anal. Calcd. for $C_{11}H_{17}NO$: C, 73.74; H, 9.50; N, 7.82. Found: C, 73.69; H, 9.01; N, 8.09.

N-(*p*-Tolyl)azetidine (IV)—Compound II was treated according to procedure C and it yielded the required azetidine (9%) at 112–118°/9 mm. The product melted at 37° after recrystallization from ethanol.

Anal. Calcd. for $C_{10}H_{13}N$: C, 81.63; H, 8.84; N, 9.52. Found: C, 81.2; H, 8.85; N, 9.84.

Compound IV formed a picrate, m.p. 122–123°.

Anal. Calcd. for $C_{16}H_{16}N_4O_7$: C, 51.06; H, 4.26; N, 14.89. Found: C, 51.49; H, 4.56; N, 14.50.

On warming IV with excess of methyl iodide, the amine ring cleaved to yield N,N-dimethyl-N-(3-iodopropyl)-N-(*p*-tolyl) ammonium iodide, m.p. 136°.

Anal. Calcd. for $C_{12}H_{19}I_2N$: C, 33.41; H, 4.41; N, 3.25: Found: C, 33.45; H, 4.67; N, 2.70.

From compound III, by procedure C, was obtained a very small sample of presumed N-(*p*-chlorophenyl)azetidine, m.p. 34–37° The quantity was insufficient for further purification and analysis, and the compound was identified through its infrared spectrum. In this reaction N-(3-ethoxypropyl)-*p*-chloroaniline, $n^{19}D$ 1.5472, b.p. 128–130°/13 mm., was obtained in 24% yield, and identified through its infrared spectrum and by analysis.

Anal. Calcd. for $C_{11}H_{16}ClNO$: C, 61.83; H, 7.49; N, 6.56. Found: C, 62.26; H, 7.63; N, 6.55.

Azetidine.—The procedure was that of Vaughan, *et al.*, and from 75 g. of *p*-toluenesulphonazetidide the average yield (over five preparations) of separated, dried amine layer was 13 g. The combined amine layers (65 g.) were fractionally distilled to give 27 g. of azetidine (b.p. 61°, $n^{25}D$ 1.4220). Also isolated was 21 g. of octahydro-1,5-diazocine, boiling over the range 186–190°, with $n^{25}D$ 1.4488, and yielding a dipicrate melting, with decomposition at 224°. A monopicrate was obtained when equimolar, hot ethanolic solutions of the amine and picric acid were mixed. This picrate had m.p. 168–169°.

Anal. Calcd. for $C_{12}H_{17}N_5O_7$: C, 41.9; H, 4.99; N, 20.41. Found: C, 41.4; H, 5.18; N, 20.49.

The octahydrodiazocine did not arise from the presence of N,N′-bis(*p*-toluenesulphonyl)octahydro-1,5-diazocine in the *p*-toluenesulphonazetidide. During the preparation of the latter from 1,3-dibromopropane (as in ref. 4a), dimer was indeed formed, m.p. 209–211°. Molecular weight determinations, by depression of freezing point of benzene, gave values of 456, 407, and 398, the determinations being limited in accuracy by the sparing solubility of the compound in benzene.

Anal. Calcd. for $C_{20}H_{26}N_2O_4S_2$: C, 56.84; H, 6.20; N, 6.63. Found: C, 56.64; H, 5.74; N, 6.01.

The dimer is only sparingly soluble in ethanol, and was therefore separated readily from *p*-toluenesulphonazetidide before the final reduction to azetidine.

N-Arylazetidines by Nucleophilic Displacement.—The general procedure was to dissolve the haloaromatic compound in ten equivalents of azetidine and to keep the mixture in a sealed tube at 50°. The tube contents were then extracted with 10% potassium hydroxide and the residue recrystallized from ethanol. Specific results were as follows:

(i) *p*-Bromonitrobenzene (0.36 g.) gave 0.29 g. of N-(*p*-nitrophenyl)azetidine as fine yellow needles, m.p. 119°.

Anal. Calcd. for $C_9H_{10}N_2O_2$: C, 60.65; H, 5.65: N, 15.74. Found: C, 60.41; H, 5.78; N. 15.52.

In this experiment crystals were deposited after 15 min., but the reaction tube was left for 50 hr. before extraction.

(ii) With *p*-chloronitrobenzene (0.22 g.), crystals were observed after 40 hr. but a further 40 hr. were allowed before extraction. The yellow crystals (0.2 g.) of N-(*p*-nitrophenyl)azetidine had m.p. 118.5°, unchanged by admixture with the product from the previous experiment.

(iii) Although *o*-bromonitrobenzene (0.31 g.) dissolved in azetidine to give a yellow solution that slowly turned orange, no crystals were deposited from the solution. After 10 days, dilute potassium hydroxide was added and the precipitated orange solid was recrystallized from petroleum ether (b.p. 50–70°). The orange crystals (0.1 g.) of N-(*o*-nitrophenyl)azetidine melted at 53.5°.

Anal. Calcd. for $C_9H_{10}N_2O_2$: C, 60.65; H, 5.65; N, 15.74. Found: C, 61.28; H, 6.10; N, 15.41.

(iv) The reaction mixture containing 3-methyl-4-nitrobromobenzene (0.12 g.) was left for 7 days; although a few small crystals had appeared after 20 hr. the quantity did not increase. The recrystallized N-(3-methyl-4-nitrophenyl)azetidine weighed 0.08 g. and had m.p. 67–68°.

Anal. Calcd. for $C_{10}H_{12}N_2O_2$: C, 62.48; H, 6.30; N, 14.29. Found: C, 62.20; H, 6.63; N, 14.03.

(v) Reaction with 1-chloro-2,4-dinitronaphthalene (0.25 g.) was immediate and gave a deep red solution and a yellow solid. The orange 1-(N-azetidino)-2,4-dinitronaphthalene, sepa-

rated after 15 hr. reaction time at 25° and recrystallized from benzene, weighed 0.11 g. The crystals, although turning black slowly on heating, melted sharply at 209–210°.

Anal. Calcd. for $C_{13}H_{11}N_3O_4$: C, 57.12; H, 4.03; N, 15.38. Found: C, 56.97; H, 4.39; N, 15.1.

(vi) 5-Bromo-2-nitroanisole (0.33 g.) and azetidine yielded crystals after 30 hr. After a total of 50 hr. the mixture was worked up to yield 0.16 g. of yellow needles melting at 123°. Analysis indicated the compound to be 2,4-bis(N-azetidino)-nitrobenzene.

Anal. Calcd. for $C_{12}H_{15}N_3O_2$: C, 61.76; H, 6.48; N, 18.01. Found: C, 62.03; H, 6.65; N, 17.72.

(vii) With 3,4-dinitrobromobenzene (0.25 g.) orange crystals were observed after 60 hr., and after a total of 110 hr. the reaction mixture was worked up to yield 0.12 g. of yellow product with m.p. 122°, unchanged when mixed with the product from vi.

Anal. Found: C, 61.07; H, 6.61; N, 17.53.

The infrared spectra of the products from vi and vii were identical.

(viii) Bromobenzene, *p*-bromochlorobenzene, and 2-bromonaphthalene were recovered from their respective reaction mixtures after 100 days at 50°.

(ix) Reactions involving *m*-bromonitrobenzene and 3,5-dinitrobenzene were similar in behavior. Reaction mixtures reddened rapidly, especially in the case of the dinitro compound. Quenching the reaction in the early stages allowed only the starting material to be isolated in each case, with an amount of intractable material which increased with time. After 100 days the mononitro compound had been converted almost entirely to a brown gummy material which did not dissolve in any common solvent. After 21 days, the dinitro compound had been completely replaced by a black solid with solubility characteristics as unhelpful as in the other case.

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The Brominative Decarboxylation of Bicyclo[2.2.2]octane-1-carboxylic Acid in Halogenated Solvents[1]

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The brominative decarboxylation of bicyclo[2.2.2]octane-1-carboxylic acid in the presence of mercuric oxide in carbon tetrachloride yields appreciable quantities of both 1-chloro- and 1-bromobicyclo[2.2.2]octane. Even in bromotrichloromethane some 1-chlorobicyclo[2.2.2]octane is formed. These results are readily interpreted on the basis of a free radical mechanism. The intermediate 1-bicyclo[2.2.2]octyl free radical is apparently sufficiently reactive to abstract chlorine rather than bromine from bromotrichloromethane. The addition of a mixture of acid and mercuric oxide to excess bromine in bromotrichloromethane provides the desired 1-bromobicyclo[2.2.2]octane free of contamination by the chloride. It was also found that the pure bromide was obtained by reaction in 1,2-dibromoethane. The reaction of the acid and oxide with iodine in carbon tetrachloride yields 1-bicyclo[2.2.2]octyl bicyclo[2.2.2]octane-1-carboxylate and 1-chlorobicyclo[2.2.2]octane.

The Hunsdiecker reaction, the decarboxylation of the silver salt of a carboxylic acid in the presence of molecular halogen, frequently is a valuable method for the introduction of halogens.[3] Recently, Cristol and Firth demonstrated that the use of mercuric oxide with the carboxylic acid possessed considerable advantage obviating the necessity for fully anhydrous conditions.[4] We attempted to apply this reaction for the synthesis of 1-bromobicyclo[2.2.2]octane. However, the adoption of conventional conditions, *i.e.*, the addition of bromine to the mercuric oxide–carboxylic acid mixture in refluxing carbon tetrachloride, yielded a mixture of 1-chloro- and 1-bromobicyclo-[2.2.2]octane. A search of the literature revealed that such side reactions leading to important quantities of impurities had previously been encountered in the Hunsdiecker reaction. For example, Dauben and Tilles observed chlorobenzene among the products of brominative decarboxylation of silver benzoate in carbon tetrachloride.[5] Similarly, Roberts and Chambers noted that chlorine containing substances were formed in the application of the Hunsdiecker reaction to cyclopropane carboxylic acid in tetrachloroethane.[6] Wilder and Winston reported the treatment of the silver salt of apocamphane-1-carboxylic acid with bromine in carbon tetrachloride yielded a mixture of substances which contained both chlorine and bromine.[7] Unfortunately, these workers were unable to characterize the products of the side reactions. The potential utility of the Hunsdiecker reaction in future studies in this laboratory led us to investigate the process in more detail.

Results and Discussion

Under the conditions suggested by Cristol and his students,[4] the addition of bromine to a mixture of red mercuric oxide and bicyclo[2.2.2]octane-1-carboxylic acid in refluxing carbon tetrachloride yielded a waxy solid with a broad melting range. Several sublimations did not significantly improve the melting behavior of the material. Vapor phase chromatography revealed the reaction product was a complex mixture of two major and four lesser components. (The four lesser compounds are discussed in the Experimental.) The two substances formed in high yield comprised more than 80% of the mixture and accounted for 75–85% of the starting bicycloöctane. These compounds were eluted from the column and their melting points and spectra obtained. Comparison with authentic materials revealed them to be the expected 1-bromo- and the unexpected 1-chlorobicyclo[2.2.2]octane. Even more unexpected was the product distribution favoring the chloride (68%) over the bromide (32%).

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(2) Esso Educational Foundation Fellow, 1961–1962.

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