20, 110, 370, and 540 min. The addition of either acid or alkali to an old catalyst increased the rate of reduction. Thus a catalyst that brought about reduction in 510 min. in neutral solution, required 141 min. when two drops of 6*N* acetic acid was added, and 71 min. when two drops of 6*N* sodium hydroxide was added. The same effects were noted when ethanol was used as a solvent.

Solutions after reduction in the mixed solvent, using either Adams catalyst or Raney nickel, always were pale yellow and recrystallization from ethanol gave brown plates melting at 76–78°. Attempts to decolorize the solutions with Norit only intensified the color. To obtain pure material the product was distilled at 150–151° at 3 mm. The distillate was crystallized from a concentrated solution in ethanol to give colorless plates, m.p. 79–80°. Melting points of 80–81° and of 81° have been recorded.[1,5]

Recently the hydrogenation of benzo[*c*]cinnoline to 2,2′-diaminobiphenyl using Raney nickel catalyst was reported.[6] During the course of the present work benzo[*c*]cinnoline-5,6-dioxide was hydrogenated to benzo[*c*]cinnoline using either Raney nickel or Adams catalyst, but further reduction to 2,2′-diaminobiphenyl did not take place.

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Conversion of 1,6-Di-*O*-methylsulfonyl-2,4:3,5-di-*O*-methylene-L-iditol to D-*threo*-4,8-Dimethylene-1,3,5,7-naphthodioxane

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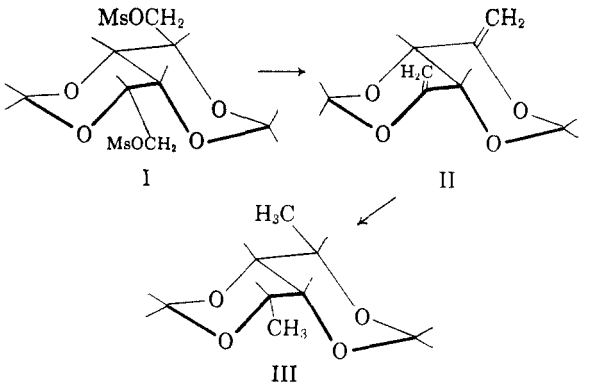
While formation of double bonds through loss of the elements of an alkyl or aryl sulfonic acid from adjacent carbon atoms under alkaline conditions has been reported repeatedly as an unwanted side reaction in the carbohydrate field,[2] the phenomenon has not received the study it deserves. We wish to report the very facile formation of the diene II from the dimesyl ester of the well-known 2,4:3,5-di-*O*-methylene-L-iditol (I).[3]

The structure of the diene was demonstrated through hydrogenation to 1,6-dideoxy-2,4:3,5-di-*O*-methylene-L-iditol (III), a substance which Hann and Hudson[3] have prepared through reduction of 1,6-dideoxy-1,6-diiodo-2,4:3,5-di-*O*-methylene-L-iditol. It is noteworthy that the diequatorial product III rather than the corresponding D-mannitol or D-glucitol analogs were isolated after the reduction of II. A crystalline tetrabromide prepared from



II is also reported here. Conformational and mechanistic considerations indicate that both the bromomethyl groups in this substance are probably equatorial although evidence on this point is lacking.

EXPERIMENTAL[4]

1,6-Di-O-methylsulfonyl-2,4:3,5-di-O-methylene-L-iditol (I). 2,4:3,5-Di-*O*-methylene-L-iditol (16.5 g.), prepared by the method of Hann and Hudson,[3] was "mesylated" in pyridine solution with methanesulfonyl chloride in normal fashion to yield a crystalline product which, recrystallized from acetone-pentane, 2-butanone, and methyl Cellosolve amounted to 20.0 g. (69%). The pure product melted at 163–164°, $[\alpha]_D^{20}$ +26° in chloroform (*c* 0.8).

Anal. Calcd. for $C_{10}H_{18}O_{10}S_2$: C, 33.14; H, 5.01; S, 17.70. Found. C, 33.37; H, 5.37; S, 17.70.

D-threo-4,8-Dimethylene-1,3,5,7-naphthodioxane (II). 1,6-Di-*O*-methylsulfonyl-2,4:3,5-di-*O*-methylene-L-iditol (6.28 g.) was added to 30 ml. of dry methyl Cellosolve in which 0.95 g. of sodium had been dissolved and the resulting mixture refluxed for 20 min. One volume of benzene and one of ether were added to the cooled reaction mixture and the sodium mesylate (4.16 g., quantitative) removed after further cooling to 0°. The filtrate, diluted with more benzene, was washed twice with water, dried over sodium sulfate, and concentrated *in vacuo* at room temperature. The crystalline residue, recrystallized twice from dichloromethane-pentane at Dry-Ice temperature and dried briefly *in vacuo* (30 mm.) at 20°, weighed 1.7 g. (58%), m.p. at 80°, $[\alpha]_D^{20}$ +269.5° in acetone (*c* 0.56). The product has a significant vapor pressure and prolonged drying results in considerable loss.

Anal. Calcd. for $C_8H_{10}O_4$: C, 56.46; H, 5.92. Found: C, 56.36; H, 5.89.

The infrared absorption spectrum of the diene showed the absence of hydroxyl and carbonyl functions and had bands at 3.5 and 3.6 μ (C—H stretching) and 6.0 μ (C=C).

1,6-Dideoxy-2,4:3,5-di-O-methylene-L-iditol (III). D-*threo-4,8-Di-methylene-1,3,5,7-naphthodioxane* (230 mg.) was dissolved in 3 ml. of glacial acetic acid and hydrogenated at 25°, platinum from 30 mg. of PtO_2 being used as catalyst. When the calculated quantity of hydrogen had been absorbed (35 min.) warm ethyl acetate was added to dissolve the partially precipitated product. The catalyst was removed and the solution concentrated *in vacuo* to a dry, crystalline

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(4) Melting points are corrected.

mass. Recrystallized from carbon tetrachloride the product (130 mg., 55%) melted at 208–210° either alone or in admixture with an authentic sample of 1,6-dideoxy-2,4-3,5-di-*O*-methylene-L-iditol.[3]

9,10-D-threo-4,8-Dibromo-4,8-di(bromomethyl)-1,3,5,7-naphthodioxane hexane. A solution of 470 mg. of the diene, II, in 5 ml. of carbon tetrachloride was treated at 0° with 7 ml. of a 4% (v/v) solution of bromine in the same solvent. The slight excess of bromine, together with the solvent was immediately removed *in vacuo* and the crystalline residue dissolved in hot cyclohexane. The resulting solution was treated with a trace of solid sodium bicarbonate and of alumina, filtered and diluted with pentane. At 0° the substance crystallized as elongated plates melting (after darkening at *ca.* 120°) at 135–150° and showing in acetone (*c* 3.35) $[\alpha]_D^{20}$ +210.0° (987 mg., 73%). After three recrystallizations from cyclohexane-pentane the material melted as before; $[\alpha]_D^{20}$ +208.1° in acetone (*c* 2.94).

Anal. Calcd. for $C_8H_{10}O_4Br_4$: Br, 65.26. Found: Br, 65.07.

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Preparation of Mono-*N*-alkyl and -*N*-Acyl Piperazines by Non-Hydrolytic Cleavage of 1-Carbethoxypiperazines

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Recent discoveries have made piperazine derivatives important as medicinal agents, and a large number of 1,4-unsymmetrically substituted piperazines has been prepared for various purposes. Among them, a promising agent for the treatment and prophylaxis of both hemorrhagic[4] and heat shock[5] is the relatively simple structure, 1-ethyl-4-ethylsulfonylpiperazine. Because of the tedious method of synthesis available for this compound, an improved procedure was sought. Specifically, the use of a nonhydrolytic cleavage of 1-carbethoxy-4-substituted piperazines which would permit the preparation of both 1-alkyl and 1-acyl piperazines was investigated.

The hydrolytic procedures which have been described for decarbethoxylation of piperazine monourethans require conditions too drastic for use in the presence of other hydrolyzable functions such as amides or esters. Use of the benzyl group as a blocking agent for piperazines is also undesirable in cases where other groups may be reduced or may poison the catalyst during catalytic debenzylation. A mild, nonhydrolytic, nonreductive decarbethoxylation was therefore attempted with dry hydrogen bromide in glacial acetic acid. This reagent has previously been used for the removal of carbobenzoxy groups in peptides[6,7] and was found suitable for the preparation of mono-*N*-alkyl piperazines. For example, 1-carbethoxy-4-ethylpiperazine was cleaved to 1-ethylpiperazine dihydrobromide in 3 hr. with an 89% yield. The monosubstituted piperazines prepared by this method are shown in Table I. 1-Isopropylpiperazine dihydrobromide was also obtained but could not be satisfactorily purified.

To investigate the suitability of the hydrogen bromide cleavage method for 1-acylpiperazines, 1-benzoyl-4-carbethoxypiperazine was first selected. When a basic aqueous solution of 1-carbethoxypiperazine was treated with an excess of benzoyl chloride at room temperature, however, a good yield of 1,4-dibenzoylpiperazine resulted. This result is in contrast to the relatively slow hydrolysis of the carbethoxy group observed in either acid or alkali. The 1-benzoyl-4-carbethoxypiperazine was obtained by treatment with benzoyl chloride in pyridine, and the cleavage with hydrogen bromide was carried out at a temperature of 60–70° for 30 min. The product was found to be piperazine dihydrobromide, however.

Similar results were obtained using 1-carbethoxy-4-acetylpiperazine and 1-carbethoxy-4-benzenesulfonylpiperazine; both the carbethoxy and acyl groups were cleaved in each instance. No indication of cleavage was apparent, from the liberation of ethyl bromide and carbon dioxide gases, until a temperature of 60–70° was reached, which prevented the use of lower temperatures for this reaction. Reduction of the reaction time to a period of 5 to 10 min. (using quantities of 0.005 mole of substituted piperazine) also resulted in the formation of piperazine dihydrobromide, either pure or admixed with starting material.

A fair yield of a monoacyl piperazine was secured, however, from the cleavage of 1-carbethoxy-4-ethylsulfonylpiperazine. After removal of the piperazine dihydrobromide and several recrystallizations, a 39% yield of 1-ethylsulfonylpiperazine hydrobromide was obtained. Further search for optimum conditions for this cleavage has not been made, since the use of 1-carbobenzyloxypiperazines appeared more suitable and is presently being investigated for the preparation of 1-acylpiperazines.

No cleavages were observed at room tempera-

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