[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

The Synthesis of 1,1,2-Trimethyl-5,6-methylenedioxyindane from Safrole

BY RUBY MURRAY ORCUTT AND MARSTON TAYLOR BOGERT

Supplementing our previous work in the indane group,[1] some experiments have been carried out with safrole (I) and isosafrole (VIII), which have led to a simple synthesis of 1,1,2-trimethyl-5,6-methylenedioxyindane by the following steps.

FLOW SHEET ($R = CH_2(O)_2C_6H_3-$)

(I) $RCH_2CH{=}CH_2 + HBr \longrightarrow$ (III) (IV)

(II) $RCH_2CHBrMe + Mg + H_2O \longrightarrow RCH_2CH(OH)Me + (RCH_2CHMe-)_2$

$RCH_2CHBrMe + Mg + AcMe \longrightarrow RCH_2CH(OH)Me + (RCH_2CHMe-)_2 +$

(V) $RCH_2CHMeC(OH)Me_2 \xrightarrow{+H_2SO_4}$

$\downarrow +H_2SO_4$

(VI) $RCH_2CMe{=}CMe_2 \xrightarrow{+H_2SO_4}$ $CH_2(O)_2C_6H_2(CH_2)(CMe_2)CHMe$ (VII)

(VIII) $RCH{=}CHMe + HBr \longrightarrow RCHBrEt$ (IX)

(X) $RCHO + EtMgBr \longrightarrow RCH(OH)Et + (RCHEt)_2O$

(XI) (XII)

Many of these compounds contain asymmetric carbon atoms and should therefore exist in optical isomers, but these stereochemical problems have not been attacked as yet.

Experimental

1-Piperonyl-1-bromoethane (II).—When a current of dry hydrogen bromide was led into carefully dried safrole, cooled to −5°, in a flask protected from access of moisture, there was a slow gain in weight up to 25% of that calculated for the addition of an equimolar quantity of hydrogen bromide. No further increase in weight occurred although the gas was passed in for several hours longer.

On working up the crude product, the yield of pure bromide (II), b. p. 145° at 9 mm., was 22%.

In another set of experiments, the safrole (25 g.) cooled to 0°, was mixed with an aqueous solution of hydrobromic acid (100 g.), saturated at 0° (or about 69% hydrogen bromide), and the mixture kept in a closed bottle at low temperature, with occasional shaking, for two or three days. The crude product was diluted with an ice-cold salt solution, the heavy bromide removed by extraction with ether, washed several times with the cold salt solution, dried over anhydrous potassium carbonate, the ether distilled off and the remainder fractionated under diminished pressure; b. p. 154–157° at 13 mm., 145° at 9 mm.; $n^{25}D$ 1.5614; yield 75%.

Anal. Calcd. for $C_{10}H_{11}O_2Br$: Br, 32.88. Found: Br, 32.82.

This process gave a very satisfactory product, with the by-products in the form of a decomposed residue easily eliminated. This secondary bromide was much more stable than the isomeric primary bromide, 2-piperonyl-1-bromoethane, described in a recent paper.[2]

In 1914, E. Merck took out a patent[3] for the manufacture of aromatic amines, in which this bromide, from safrole and aqueous hydrobromic acid, was an intermediate product, but was separated only in a crude state as a slightly colored heavy unstable oil, which decomposed when distilled *in vacuo* and was not analyzed.

1-Piperonylethanol-1 (III).—The bromide (II) was converted into the Grignard compound in the customary way, after activating the magnesium by a small crystal of iodine. The reaction, after starting rather slowly, proceeded satisfactorily, and the initial cloudiness disappeared as the reaction advanced. Due apparently to its sensitivity to oxygen, this Grignard compound tended to pass into the secondary alcohol (III) with surprising ease, even in a closed system from which all moisture had been carefully excluded, and this introduced complications in using it for the synthesis of other compounds as explained in the next section. No such difficulty was encountered[2] in the preparation of the isomeric $RCH_2CH_2CH_2MgBr$. At the close of the reaction, the mixture was warmed for thirty minutes, then cooled to 0°, stirred for two hours, hydrolyzed by acidulated ice water and worked up as usual. The crude product (8.5 g.) was distilled under reduced pressure, and yielded 4 g. of the alcohol (III) sought, b. p. 127–129° at 3 mm., 2.5 g. of a by-product of safrole-like odor and 0.5 g. of the butane derivative (IV).

In contradistinction to its primary isomer, 2-piperonylethanol-1, this alcohol showed no tendency whatever to crystallize.

Phenylurethan.—Colorless needles (from alcohol), m. p. 93–94° (uncorr.).

Anal. Calcd. for $C_{17}H_{17}O_4N$: C, 68.20; H, 5.72. Found: C, 67.87; H, 5.75.

2-Methyl-3-piperonylbutanol-2 (V) was prepared by the Grignard reaction from the bromide (II) and acetone. Due to the sensitivity of the $RCH_2CH(MgBr)Me$, mentioned above, the preparation proved more troublesome than expected.

When the experiments were conducted in the air, there were obtained from 46 g. of the bromide (II), 16 g. of safrole, 10.4 g. of the secondary alcohol (III), 3 g. of the tertiary alcohol (V), and 1 g. of the 2,3-dipiperonylbutane (IV). The figures for the two alcohols are only approxi-

(1) (a) Bogert and Davidson, THIS JOURNAL, **56**, 185 (1934); (b) Roblin, Davidson and Bogert, *ibid.*, **56**, 248 (1934).

(2) Orcutt and Bogert, *ibid.*, **58**, 2055 (1936).

(3) Merck, German Patent 274,350; *Chem. Zentr.*, **85**, I, 2079 (1914).

mate, because of the difficulty of separating these alcohols quantitatively.

The secondary alcohol (III) isolated, b. p. 127–129° at 3 mm., was analyzed with the following results.

Anal. Calcd. for $C_{10}H_{12}O_3$: C, 66.63; H, 6.72. Found: C, 66.09; H, 6.69.

Its phenylurethan crystallized from alcohol in colorless needles, m. p. 93–94°. Mixed with the phenylurethan described in the foregoing section, the m. p. was unchanged.

Anal. Calcd. for $C_{17}H_{17}O_4N$: C, 68.20; H, 5.72. Found: C, 68.10; H, 5.77.

The tertiary alcohol (V), on account of the relatively small amount present, could not be isolated in satisfactory purity.

But when the experiments were carried out in an atmosphere of nitrogen, the same amount (46 g.) of initial bromide (II) gave 17 g. of safrole, none of the secondary alcohol (III), 11 g. of the tertiary alcohol (V), and 1.5 g. of the butane derivative (IV). From this mixture, the *tertiary alcohol* was easily isolated by fractional distillation as a colorless, very viscous liquid, b. p. 142–144° at 3 mm., which congealed in thick colorless needles, m. p. 49°, with some softening as low as 43°. The isomeric 2-methyl-4-piperonylbutanol-2 differs from it in persistently remaining liquid and refusing to crystallize.

Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.23; H, 8.17. Found: C, 69.86; H, 8.37.

It did not form a phenylurethan. Phenyl isocyanate abstracted water from it, with separation of carbanilide.

2,3-Dipiperonylbutane (IV).—In the residues from the distillation of the crude products obtained in the preparation of both the secondary (III) and tertiary (V) alcohols, this by-product was found. It was purified by repeated crystallization, first from methyl and finally from ethyl alcohol, and then formed thick colorless needles or plates, m. p. 74°.

Anal. Calcd. for $C_{20}H_{22}O_4$: C, 73.58; H, 6.79. Found: C, 73.26; H, 6.53.

1,1,2-Trimethyl-5,6-methylenedioxyindane (VII).—To 20 g. of well-cooled (7°) 85% sulfuric acid, there was stirred in gradually 7 g. of the tertiary alcohol (V). The resultant reddish mixture was diluted with ice water, extracted with ether, the ether extracts dried over fused potassium carbonate, the ether removed and the residue fractionated thrice over sodium. The indane so obtained was a colorless oil, b. p. 137° at 11 mm., of penetrating camphoraceous odor; yield about 65%. It did not decolorize an acetone solution of potassium permanganate.

Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76.43; H, 7.89. Found: C, 76.15; H, 8.20.

Fused with selenium for six hours at 266–270°, a strong odor of methyl mercaptan was noted, and from the tarry product there was isolated a small quantity of a clear yellow liquid, b. p. about 140° at 7 mm., which darkened rapidly and on re-distillation exhaled an odor resembling that of the original indane. It was not obtained in sufficient amount or purity for analysis or identification, nor could a picrate be prepared from it. These results are in accordance with our previous experience with indanes.[1b]

2-Methyl-3-piperonylbutene-2 (VI).—Occasionally this olefin was isolated from the crude product of the above indane synthesis, by fractional distillation of a cyclization product which was unsaturated to an acetone solution of potassium permanganate. It formed an oil, b. p. 120° at 7 mm., colorless when freshly distilled, which rapidly turned yellow, even in a tightly sealed bottle, possessed a citrous or alliaceous type of odor, quickly decolorized an acetone solution of potassium permanganate, and did not form a picrate. For analysis, it was freshly distilled.

Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76.43; H, 7.89. Found: C, 76.21; H, 8.06.

Subjected to the further action of sulfuric acid, it was rearranged to the isomeric indane (VII).

***alpha*-Ethylpiperonyl Bromide (IX).**—This bromide appeared to be formed in good yield by the action of aqueous hydrobromic acid (69%) upon isosafrole at 0°, as described for the preparation of its isomer (II) from safrole, but it was so unstable that it decomposed when distilled at a pressure of 2 mm.

The Merck patent,[3] already mentioned, refers also to the preparation of this bromide, in an impure state, from isosafrole and hydrobromic acid, and describes it as a slightly colored heavy unstable oil, which decomposed when distilled *in vacuo*, and was not analyzed.

This patent also claims the formation of the corresponding amine when the crude bromide is treated with ammonia. When we treated our product with alcoholic ammonia, even at low temperature, a vigorous reaction ensued, with immediate separation of ammonium bromide in an amount which indicated the presence of approximately 50% of the desired bromide (IX) in the original crude.

***alpha*-Ethylpiperonyl alcohol (XI)** was prepared from piperonal (X) and ethylmagnesium bromide, as recorded by Mameli.[4] Inasmuch as the compound obtained by us (yield 50%) showed a b. p. of 126–127° at 3 mm., whereas that reported by him was 172–175° at atmospheric pressure, our product was analyzed.

Anal. Calcd. for $C_{10}H_{12}O_3$: C, 66.63; H, 6.72. Found: C, 66.77; H, 6.42.

No phenylurethan could be secured from this alcohol, because the phenyl isocyanate immediately withdrew from it the elements of water. In this respect it differed strikingly from the isomeric 1-piperonylethanol-1 (III). Nor could we prepare a benzoate from it, or convert it into the corresponding bromide by the action of phosphorus tribromide.

The pure alcohol, after standing for three months at laboratory temperature, turned cloudy and began to crystallize. Dried in an evacuated desiccator and analyzed, it proved to be the ether (XII); yield, equal to that calculated. Apparently this alcohol tends to split out a molecule of water on standing even at ordinary temperature. When warmed or distilled under reduced pressure, however, it loses water quite easily with formation of isosafrole, as found also by Mameli.[4]

Di-*alpha*-ethylpiperonyl Ether (XII).—The distillation residues from the preparation of the foregoing alcohol (XI), when crystallized from methyl alcohol, gave a 5% yield of this ether in colorless leaflets, m. p. 85°.

(4) Mameli, *Rend. Accad. Lincei*, [5] **13**, II, 315 (1904).

Anal. Calcd. for $C_{20}H_{22}O_5$: C, 70.14; H, 6.48; mol. wt. (Rast), 342.2. Found: C, 70.04, 69.85; H, 6.21, 6.42; mol. wt. (Rast), 336.3.

Mameli,[5] who was the first to describe this ether, found that it was formed when an ether solution of the alcohol was left for many weeks in contact with traces of inorganic salts, and gave its m. p. as 88°.

Summary

1. By the addition of hydrobromic acid to safrole, 1-piperonyl-1-bromoethane has been prepared and from this the corresponding alcohol.

2. The Grignard reaction applied to the bromide, in the presence of acetone, yielded a mixture of 1-piperonylethanol-1, 2-methyl-3-piperonylbutanol-2 and 2,3-dipiperonylbutane.

3. This butanol has been converted by the action of sulfuric acid into the corresponding butene and 1,1,2-trimethyl-5,6-methylenedioxyindane.

4. From isosafrole and hydrobromic acid, *alpha*-ethylpiperonyl bromide has been obtained. The corresponding alcohol, from piperonal and ethylmagnesium bromide, has been shown to lose water on standing, with formation of the ether.

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(5) Mameli, *Rend. Accad. Lincei*, [5] **13**, II, 612 (1904); *Gazz. chim. ital.*, **35**, II, 32 (1905).

[CONTRIBUTION FROM THE BURROUGHS WELLCOME AND CO., U. S. A., EXPERIMENTAL RESEARCH LABORATORIES]

Some N-Aryl Barbituric Acids. II

BY JOHANNES S. BUCK

The present work is a continuation of that described in an earlier paper.[1] Two further series of 1-aryl-5,5-dialkyl barbituric acids have been prepared, the aryl groups being, as before, phenyl, *o*-, *m*- and *p*-tolyl, *o*-, *m*- and *p*-anisyl, *o*-, *m*- and *p*-phenetyl, and α- and β-naphthyl, while the alkyl groups are now 5,5-ethyl-isobutyl and 5,5-ethyl-isoamyl. The alkyl groups were selected to allow comparison, pharmacologically, with a series of isoalkylaryl ureas at present under examination.

Since the sodium salts of the N-aryl barbituric acids show a tendency to hydrolyze in aqueous solution, a number of barbituric acids having a dialkylamino group on the phenyl ring was prepared. These compounds are soluble both in alkaline and in acid solution. The presence of the dialkylamino group should also facilitate the resolution of those barbituric acids which carry, in addition to this group, an asymmetric carbon atom.

The two phenyl compounds have been previously described by Hjort and Dox;[2] the others are new. The pharmacological data will be given later in another place.

Experimental

Ethyl isobutylethylmalonate[3] and ethyl isoamylethylmalonate[3] were prepared by the action of the isoalkyl iodide on ethyl ethylmalonate, in the presence of sodium ethylate. It was found advantageous to carry out the reaction as rapidly as possible and to shake the crude ester several times with 5% sodium hydroxide solution.[4] After fractionation under reduced pressure the isobutyl compound boiled at 128.5–130° (15 mm.) (yield 71%) and the isoamyl compound at 126–127° (7.5 mm.) (yield 64%).

The condensation of the ester with the aryl urea and the subsequent purification were carried out substantially as previously described.[1] The procedure was modified in the case of the dialkylamino compounds, the cold reaction mixture being diluted, extracted with ether when possible, and saturated with carbon dioxide to precipitate the product, which was purified by recrystallization from aqueous alcohol, and usually also from ethyl acetate–hexane. No particular trouble was encountered except with 1-*m*-phenetyl-5,5-ethyl-isoamyl barbituric acid which was very difficult to obtain crystalline.

The barbituric acids are tabulated below. They are all white, crystalline, tasteless compounds, soluble in cold 5% sodium hydroxide solution, practically insoluble in water, slightly soluble to insoluble in petroleum ether, soluble in ether, soluble in alcohol, moderately to readily soluble in benzene, and readily soluble in ethyl acetate. In addition, the dialkylamino compounds dissolve readily in 5% hydrochloric acid. The solvents used for purification are given in the order used. Three or more crystallizations were generally necessary. In the tables the appearance described is that of the bulk specimen, crystallized from the last solvent given. The appearance varies greatly with solvent, etc.

The ureas are the same as those previously used.[1] Dimethylaminophenyl urea and diethylaminophenyl urea were prepared by the action of potassium cyanate on the amine hydrochloride in aqueous solution.

(1) Buck, THIS JOURNAL, **58**, 1284 (1936).
(2) Hjort and Dox, *J. Pharmacol.*, **35**, 155 (1929).
(3) Shonle and Moment, THIS JOURNAL, **45**, 243 (1923).
(4) *Cf.* Michael, *J. prakt. Chem.*, [2] **72**, 537 (1905).