

*Analyses.* Calc. for  $C_{11}H_{21}ON_3$ : C, 62.56; H, 9.95; N, 19.91. Found: C, 62.89; H, 10.03; N, 19.87.

### Summary

It has long been recognized that a method of reducing aliphatic hydrazones, azines and semicarbazones would be of great preparative value in the case of hydrazino-, hydrazo-, and azo paraffins. Wieland in "Die Hydrazine," p. 94, sums up the efforts of chemists in this direction as follows: "The unsaturated complex  $C=N$  shows no great tendency to take up hydrogen. No positive results have been accomplished in the hydrogenation of aliphatic hydrazones, and Thiele only a short time ago showed in the case of the azines their incapability of reduction to hydrazoparaffins." Lochte and Bailey by applying catalytic reduction to the problem found that the reaction unsuccessfully attempted by Thiele can be effected with the greatest ease, and in the present paper it is shown that the same method of attack leads to the reduction of certain semicarbazones and hydrazones where other investigators have obtained only negative results.

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## AMIDE FORMATION FROM ESTERS OF SECONDARY ALKYL MALONIC ACIDS

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The striking difference in behavior of the ethyl esters of mono-alkyl- and di-alkyl-malonic acids was pointed out by Fischer and Dilthey.<sup>1</sup> According to their experiments the ethyl esters of methyl-, ethyl- and propylmalonic acids react readily with alcoholic and with liquid ammonia, giving good yields of the corresponding di-amides, together with small amounts of the intermediate ester-amides. On the other hand, the ethyl esters of dimethyl-, diethyl- and dipropylmalonic acids give under the same conditions no amide at all, or else the merest traces. The reaction obtained with the mono-alkyl derivatives was attributed by Fischer and Dilthey to the unsubstituted hydrogen which confers acidic properties upon the substance and makes possible the formation of an intermediate addition product with ammonia. This explanation was shown by Meyer<sup>2</sup> to be inadequate. Meyer found that the methyl esters of dimethyl- and methylethyl-malonic acids readily formed amides when treated with aqueous ammonia. With the methyl ester of diethyl-malonic acid, however, no amide was formed. The presence of 2 ethyl groups, whether in the side chains or in the nucleus, apparently brings about a condition of

<sup>1</sup> Fischer and Dilthey, *ibid.*, **35**, 844 (1902).

<sup>2</sup> Meyer, *ibid.*, **39**, 198 (1906).

so-called steric hindrance. Meyer<sup>3</sup> showed further that the methyl esters of di-allyl-, methylpropyl- and methylbenzyl-malonic acids react with ammonia, whereas the corresponding ethyl esters do not.

Amides of numerous alkyl-malonic acids are described in the literature. None of these, however, contains a secondary alkyl. In some respects the esters of secondary alkyl-malonic acids show an anomalous behavior. For example, the introduction of a second alkyl group is difficult and the yield is small, while the introduction of a second secondary alkyl group has not yet been accomplished by direct alkylation. Fischer and Dilthey<sup>4</sup> were unsuccessful in their attempts to prepare ethyl di-*isopropyl*-malonate, and Hope and Perkin<sup>5</sup> were likewise unable to prepare ethyl dicyclohexyl-malonate.

According to the experience of the writers, methyl esters behave in this regard exactly like the ethyl esters. We were unsuccessful in our attempts to introduce an *isopropyl* group into methyl *isopropyl*-malonate and methyl cyclohexyl-malonate, or a cyclohexyl group into methyl *iso*-propyl-malonate.

We have found that the esters of secondary alkyl-malonic acids present a similar anomaly with respect to amide formation. The ethyl esters of *isopropyl*- and *sec*.-butyl-malonic acids after frequent shaking with a large excess of conc. ammonia during a period of 2 weeks gave only small amounts of the amide, the greater part of the ester remaining unchanged. On the other hand, the corresponding methyl esters gave within 24 hours an abundant separation of crystalline amide and only traces of ester remained in the mother liquor after 3 days.

In our study of secondary alkyl-malonic acids we prepared the following derivatives which have not previously been described.

***Isopropyl-malonamide***.—Thirty g. of methyl *isopropyl*-malonate and 200 cc. of 28% aqueous ammonia were shaken vigorously in a tightly stoppered bottle and allowed to stand overnight. The next morning, a mass of crystals was observed. After standing for 24 hours the crystals were filtered off with suction and washed with ether to remove any unchanged ester. The yield was 15.4 g. Recrystallized twice from water, the substance melted at 260°. It is difficultly soluble in cold water, more soluble in hot water, and still more so in hot alcohol. From water it is obtained in crystals resembling rhombohedra.

*Analyses*. Subs., 0.2, 0.2: 27.3, 27.5 cc. of 0.1 N NH<sub>3</sub>. Calc. for C<sub>6</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub>: N, 19.44. Found: 19.12, 19.27.

**Methyl *sec*.-Butyl-malonate**.—The ethyl ester has been prepared by van Romburgh<sup>6</sup> and by Kulisch.<sup>7</sup> The former reports a boiling point of 233–234° at 774 mm. and the latter 224–225°. Our product boiled at 234–236° at 755 mm. The ethyl ester was

<sup>3</sup> Meyer, *Monatsh.*, **27**, 1083 (1906).

<sup>4</sup> Fischer and Dilthey, *Ann.*, **334**, 337 (1904).

<sup>5</sup> Hope and Perkin, *J. Chem. Soc.*, **95**, 1363 (1909).

<sup>6</sup> van Romburgh, *Rec. trav. chim. Pays-Bas*, **4**, 150 (1887).

<sup>7</sup> Kulisch, *Monatsh.*, **14**, 559–71 (1893).

converted into the methyl ester as follows. Fifty g. of the ethyl ester was heated under a reflux condenser for 2 hours with 150 cc. of absolute methyl alcohol in which 1 g. of sodium had been dissolved. The mixed methyl and ethyl alcohols were distilled *in vacuo*, and to the residue another portion of 150 cc. of methyl alcohol was added. The mixture was again refluxed and the alcohols distilled as before. The residue was made slightly acid with dil. acetic acid, and the oil which separated was washed several times by shaking it with water; finally it was dried over calcium chloride. Repeated fractionation of the oil gave 18.5 g. of a product boiling at 217–218° at 748 mm.

*Analysis.* Subs., 0.1706: CO<sub>2</sub>, 0.3635; H<sub>2</sub>O, 0.1388. Calc. for C<sub>9</sub>H<sub>18</sub>O<sub>4</sub>: C, 57.4; H, 8.5. Found: C, 58.0; H, 8.7.

*Sec.-Butyl-malonamide.*—Five g. of this methyl ester was shaken vigorously with 50 cc. of conc. ammonia and set aside for 2 days. By that time a mass of lustrous scaly crystals had formed. These were collected with the aid of suction, washed with water and then with ether and finally crystallized from dilute alcohol. The product weighed 2 g. and had a melting point of 242°. The substance is almost insoluble in cold water but readily soluble in alcohol.

*Analyses.* Subs., 0.2, 0.2: 25.35, 25.15 cc. of 0.1 N NH<sub>3</sub>. Calc. for C<sub>7</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub>: N, 17.72. Found: 17.75, 17.61.

*Methyl cyclohexyl-malonate.*—As Perkin and Hope noted in the preparation of the ethyl ester, the yield here is poor, owing mainly to the conversion of bromocyclohexane into cyclohexene. From 132 g. of methyl malonate, 165 g. of bromocyclohexane, and 23 g. of sodium dissolved in 400 cc. of absolute alcohol, we obtained after 10 hours' refluxing only 23 g. of a pure product, the boiling point of which was 121–122° at 6 mm.;  $d_{25}^{25}$  1.0737.

*Analysis.* Subs., 0.1904: CO<sub>2</sub>, 0.4318; H<sub>2</sub>O, 0.1545. Calc. for C<sub>11</sub>H<sub>18</sub>O<sub>4</sub>: C, 61.7; H, 8.4. Found: C, 61.8; H, 8.7.

*Cyclohexylm-alonamide.*—Five g. of the above ester was shaken with 50 cc. of conc. ammonia. Within 3 hours the formation of crystals was noticed. After the mixture stood for 4 days, the crystals were collected on a filter, washed with water and with ether, and recrystallized from alcohol. The yield was 2 g. of fine, scaly crystals melting at 305°. The substance is practically insoluble in water, but readily soluble in alcohol.

*Analyses.* Subs., 0.1, 0.1: 10.8, 10.7 cc. of 0.1 N NH<sub>3</sub>. Calc. for C<sub>9</sub>H<sub>16</sub>N<sub>2</sub>O<sub>3</sub>: N, 15.21. Found: 15.12, 14.98.

The alcoholic mother liquor from the above yielded about 1 g. of needle-shaped crystals melting at 169°. They were practically insoluble in water but considerably more soluble in alcohol than was the amide. The nitrogen content was 8.09%. This approximates the nitrogen content of an imide which would result from the amide by loss of ammonia. Unlike most imides, however, the substance was insoluble in dil. sodium hydroxide solution. We have not examined it further.

*Phenyl-malonamide.*—Wislicenus and Goldstein<sup>8</sup> attempted to prepare this amide by heating ethyl phenylmalonate with alcoholic ammonia in a sealed tube at water-bath temperature. The product was identified as the ester-amide, melting at 152°. Another product, insoluble in benzene, was also obtained, which they suspected to be the di-amide, but the amount was too small for identification, and no melting point was reported.

Since methyl phenylmalonate is a solid, it was first dissolved in 20 cc. of alcohol and then 50 cc. of conc. aqueous ammonia was added. At first a turbidity resulted, then an oil separated which almost immediately became crystalline. From 5 g. of the ester

<sup>8</sup> Wislicenus and Goldstein, *Ber.*, **29**, 2602 (1896).

the yield of amide was 3 g. in 24 hours. The substance was insoluble in cold water and readily soluble in alcohol. Recrystallized from alcohol it melted at 233°.

*Analyses.* Subs., 0.2, 0.2: 22.4, 22.5 cc. of 0.1 *N* NH<sub>3</sub>. Calc. for C<sub>9</sub>H<sub>10</sub>N<sub>2</sub>O<sub>2</sub>: N, 15.72. Found: 15.68, 15.75.

Similar experiments with the ethyl esters of *isopropyl*, *sec.*-butyl-, and cyclohexyl-malonic acids showed the amide formation in this case to be extremely slow. Even after the mixtures had stood for two weeks, only a few crystals were observed, most of the ester remaining unchanged. The largest yield was obtained from the *sec.*-butyl derivative and this amounted to less than 5% of the calculated amount. Alcoholic ammonia and liquid ammonia were not tried. In all probability the same difference in the rate of amide formation between the methyl and ethyl esters would prevail as was observed with aqueous ammonia.

*Sec.*-alkyl-barbituric acids corresponding to the esters described above have not previously been recorded. In preparing these we used the ethyl esters, which we condensed with urea in the presence of an excess of sodium ethylate at about 105°. The details of the method are practically those of the original veronal synthesis and are too familiar to require repetition.

**5-*Sec.*-butyl-barbituric acid.**—From 11 g. of the ester, 6 g. of the barbituric acid was obtained. The substance is somewhat soluble in water and in benzene and readily soluble in alcohol and in dil. alkalies. From alcohol it was obtained in pearly scales melting at 199°.

*Analyses.* Subs., 0.2, 0.2: 21.6, 21.5 cc. of 0.1 *N* NH<sub>3</sub>. Calc. for C<sub>8</sub>H<sub>12</sub>N<sub>2</sub>O<sub>3</sub>: N, 15.22. Found: 15.12, 15.05.

**5-Cyclohexyl-barbituric acid.**—In this and in the following preparation, an accident resulted in the loss of some of the material; hence the yields are not reported. The product was very similar in appearance and solubility to the preceding. It melted at 254-256°.

*Analyses.* Subs., 0.2, 0.2: 18.95, 18.85 cc. of 0.1 *N* NH<sub>3</sub>. Calc. for C<sub>10</sub>H<sub>14</sub>N<sub>2</sub>O<sub>3</sub>: N, 13.33. Found: 13.27, 13.15.

**5-Cyclohexyl-2-thio-barbituric acid.**—This preparation was made simultaneously with the preceding, using thio-urea in place of urea. The product consisted of small flat needles of a pale yellow color. It melted at 188-189°.

*Analyses.* Subs., 0.1, 0.1: 9.0, 8.8 cc. of 0.1 *N* NH<sub>3</sub>. Subs., 0.2162, 0.2058: BaSO<sub>4</sub>, 0.2241, 0.2178. Calc. for C<sub>10</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub>S: N, 12.38; S, 14.16. Found: N, 12.60, 12.53; S (Carius), 14.24, 14.53.

## Summary

Fischer and Dilthey's observation on the difference in rate of amide formation from ethyl esters of mono- and di-alkyl-malonic acids, and Meyer's observation on the difference in rate of amide formation from methyl and ethyl esters of di-alkyl-malonic acids, have been extended to include the methyl and ethyl esters of *sec.*-alkyl-malonic acids. With respect to amide formation, the secondary alkyl-malonic esters were found to resemble the di-alkyl-malonic esters. Several new amides and barbituric acids derived from *sec.*-alkyl-malonic acids are described.

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