nearly to dryness, an additional 1.7 g. of salt was obtained. These fractions were purified separately by recrystallization from ethyl acetate to constant rotation; less-soluble salt, white crystals, m. p. 194° (cor.) with decomposition; more-soluble salt, white crystals, m. p. 132° (cor.) with decomposition.

Anal. Calcd. for $C_{15}H_{13}O_2Cl\cdot C_{20}H_{24}O_2N_2$: C, 71.82; H, 6.38. Found: less-soluble salt: C, 71.54; H, 6.59; more-soluble salt: C, 71.98; H, 6.46.

Rotations. Less-soluble salt: 0.018 g. made up to 10 cc. with ethanol at 26° gave α_D −0.140°; *l*, 1; $[\alpha]^{26}_D$ −72°. More-soluble salt: 0.017 g. made up to 10 cc. with ethanol at 26° gave α_D −0.23°; *l*, 1; $[\alpha]^{26}_D$ −136°.

***d*- and *l*-β-Chloro-β-(2-methyl-1-naphthyl)-α-methylacrylic Acids.**—The acids were obtained from their salts in the manner described for the β-chloro-β-(2-methyl-1-naphthyl)-acrylic acids except that it was not necessary to extract aqueous solutions of their sodium salts with chloroform. Recrystallized from petroleum ether (b. p. 60–110°); *d*-acid, white crystals, m. p. 123° (cor.); *l*-acid, white crystals, m. p. 123° (cor.).

Anal. Calcd. for $C_{15}H_{13}O_2Cl$: C, 69.06; H, 5.03. Found: *d*-acid: C, 69.02; H, 5.19; *l*-acid: C, 69.41; H, 5.15.

Rotations. *d*-Acid: 0.020 g. made up to 10 cc. with ethanol at 26° gave α_D +0.11°; *l*, 1; $[\alpha]^{26}_D$ +55°. *l*-Acid: 0.024 g. made up to 10 cc. with ethanol at 26° gave α_D −0.14°; *l*, 1; $[\alpha]^{26}_D$ −58°.

Racemization of *l*-β-Chloro-β-(2-methyl-1-naphthyl)-α-methylacrylic Acid.

Rotations. 0.100 g. of acid made up to 25 cc. with *n*-butanol at 30° gave α_D −0.54°; after refluxing for thirty-four and one-quarter hours, −0.38°; sixty-two hours, −0.30°; one hundred five hours, −0.225°; one hundred thirty-six hours, −0.13°.

The half-life period calculated on the basis of a unimolecular reversible reaction is around seventy hours.

Summary

1. β-Chloro-β-(2-methyl-1-naphthyl)-acrylic acid and β-chloro-β-(2-methyl-1-naphthyl)-α-methylacrylic acid have been prepared and resolved. The rate of racemization of the active forms was determined and the half-life values compared with those of the corresponding bromomesitylene derivatives with similar side chains. The results demonstrate that the methyl group is more effective in producing restriction than the —CH= grouping of an aromatic nucleus.

2. The α-acyl-β-methylnaphthalenes used as starting materials in the syntheses were most satisfactorily synthesized as follows: α-bromo-β-methylnaphthalene → β-methyl-α-naphthoic acid → β-methyl-α-naphthoyl chloride → α-acyl-β-methylnaphthalene.

URBANA, ILLINOIS RECEIVED AUGUST 4, 1941

[CONTRIBUTION FROM THE GEORGE HERBERT JONES CHEMICAL LABORATORY OF THE UNIVERSITY OF CHICAGO]

The Oxygen Effect in the Reaction of Bromine with Neopentane, *t*-Butylbenzene and Trimethylacetic Acid

BY M. S. KHARASCH AND MORTON Z. FINEMAN

Preliminary work in this Laboratory has shown that tertiary hydrogen atoms are more readily replaced by bromine atoms than are secondary hydrogen atoms.[1] Because of these observations, it was decided to investigate the bromination of compounds containing primary hydrogen atoms.

A search of the literature revealed that aliphatic compounds containing only primary hydrogen atoms have hitherto been brominated only at elevated temperatures. Most of the reactions were carried out in the gas phase.[2] The only reported low temperature liquid phase bromination of a compound containing only primary hydrogen atoms is that of Colibasi petroleum boiling at 0–10°; this material contained neopentane, but the range of its boiling point indicates that it was a mixture of hydrocarbons.[3] Moreover, although the refractive index of the reaction product agrees with that of neopentyl bromide (prepared by Whitmore, Wittle and Harriman[4]), the large discrepancies in boiling point and in density suggest a mixture of brominated hydrocarbons.[5] Because of these discrepancies, it was decided to investigate the liquid phase bromination of neopentane, *t*-butylbenzene and trimethylacetic acid.

Results

The results indicate that pure neopentane does not react with dilute solutions of bromine at room temperature even under optimum conditions,

---

[1] Hered, Ph.D. Dissertation, University of Chicago.

[2] (a) Egloff, Schaad and Lowry, Jr., *Chem. Rev.*, **8**, 58 (1931); (b) Perelis, *Ind. Eng. Chem.*, **25**, 1160 (1933).

[3] Poni, *Chem. Zentr.*, **77**, I, 442 (1906).

[4] Whitmore, Wittle and Harriman, THIS JOURNAL, **61**, 1585 (1939).

[5] *Cf.* the physical constants obtained by the two investigators: Poni: b. p. 89–91 (749 mm.); $d^{20.4}_0$, 1.260; n_D 1.4369; Whitmore: b. p. 105 (732 mm.); d^{20}_4, 1.199; n_D 1.4370.

i. e., in the presence of oxygen or peroxides and under illumination. At higher temperatures, the bromination, though still very slow, is accelerated by light, oxygen and peroxides.

TABLE I

THE REACTION OF BROMINE AND NEOPENTANE[a,b,c]

Added substances	Oxygen pressure, cm.	Light	Reaction time, hr.	% Reaction
None	*Vacuo*	+	30	0
None	0.5	+	63	100
None	5	+	13	10
None	10	+	43	100
None	15	+	18	100
None	15	−	20	0
Ascaridole 0.01[d]	*Vacuo*	+	32	100
Ascaridole 0.01[d]	5	+	12	100
Lauryl peroxide 0.01[d]	5	−	50	0
Lauryl peroxide 0.01[d]	5	+	21	100

[a] The mole ratio of bromine to neopentane was 1:44. [b] Other experiments where direct sunlight was the source of illumination gave the following results. In the presence of 15 cm. of oxygen, where the mole ratio of bromine to neopentane was 1:44, the reaction was complete in six hours; under the same conditions, save that the mole ratio was 1:2, no reaction occurred within two months. [c] Temperatures were 80° except where indicated. [d] Quantities expressed in moles per mole of bromine used. These experiments were performed at 50°. A blank run using carbon tetrachloride in place of neopentane gave no evidence of reaction.

The effect of light and oxygen is brought out strikingly in experiments carried out at 80°. In the presence of oxygen complete reaction occurs in eighteen hours under illumination, while no bromination occurs in twenty hours in the absence of this reagent (Table I). Since only small quantities of material were used, the products of each reaction could not be identified. Attempts to prepare larger amounts of material by using more concentrated solutions of bromine in neopentane (1:2 moles, respectively) resulted in no reaction even under optimum conditions (three hundred hours in the light).

Reformatsky[6] was unable to obtain bromotrimethylacetic acid by the action of bromine on trimethylacetic acid or its acid chloride in the presence of phosphorus; at higher temperatures a mixture of brominated hydrocarbons was obtained. We find that bromine does not react with trimethylacetic acid under optimum conditions for the bromination of neopentane. At a temperature of 150°, a slow reaction takes place in the dark. An experiment using bromine and trimethylacetic acid in the molar ratio of 1:2 gave the following products: (1) hydrogen bromide, (2) carbon dioxide, (3) a mixture of brominated hydrocarbons, (4) nine per cent. of a material identified as trimethylacetoxytrimethylacetic acid, $(CH_3)_3CCO_2CH_2C(CH_3)_2COOH$. No carbon monoxide was formed in the reaction.

The side-chain bromination of *t*-butylbenzene has not hitherto been reported. At 80° in the presence of oxygen and under illumination (the optimum conditions for the bromination of neopentane), only the nuclear-brominated product was formed.

Discussion

It is evident from the experiments just described that pure neopentane and bromine react slowly even under optimum conditions. The fact that the extremely slow reaction is accelerated by illumination and by oxygen or peroxides indicates a chain mechanism which may involve the following steps

$$\left.\begin{array}{ll}(1) & Br_2 + h\nu \longrightarrow 2Br\cdot \\ (2) & Me_4C + O_2 + \text{light} \longrightarrow \\ & \qquad\qquad (CH_3)_3CCH_2\cdot + \cdot HO_2 \\ (3) & HBr + O_2 \longrightarrow \cdot HO_2 + Br\cdot \end{array}\right\} \text{Chain initiating reactions}$$

$$\begin{array}{ll}(4) & (CH_3)_3CCH_3 + Br\cdot \longrightarrow (CH_3)_3CCH_2\cdot + HBr \\ (5) & (CH_3)_3CCH_2\cdot + Br_2 \longrightarrow (CH_3)_3CCH_2Br + Br\cdot \end{array}$$

Reaction (5) is probably exothermic and requires little or no activation, whereas reaction (4) probably requires considerable activation energy.

The fact that at room temperature tertiary and secondary hydrogen atoms are readily replaced by bromine, whereas primary hydrogen atoms are resistant to bromination, indicates that the differences in energy of activation of tertiary, secondary and primary hydrogen–carbon bonds may critically affect the rate of reaction (4). At room temperature, these differences in the activation energy may limit the length of the chain in the given set of reactions, thus increasing the effects of the competing atom removing mechanisms. This explanation is significant in view of the retardation of the reaction by high bromine concentrations, which is especially marked in the reaction with neopentane.

Consideration of a similar chain mechanism in the chlorination of aliphatic hydrocarbons shows that the reaction corresponding to (4) would be exothermic and would require little activation, regardless of the nature of the alkyl radical. At higher temperatures, therefore, the ratio of the amounts of chlorine substitution on primary, secondary and tertiary carbon atoms should

---

[6] Reformatsky, *Ber.*, **23**, 1594 (1890).

closely approach 1:1:1 and such seems to be the fact.[7]

In vapor phase bromination at high temperatures where bromine atoms may easily acquire the necessary activation energy, mixtures of normal and secondary brominated products are obtained.[2b] In the present work an elevation in temperature was found necessary for the bromination of neopentane.

The ready bromination of toluene in the side chain, as contrasted to the exclusively nuclear bromination of *t*-butylbenzene, proves that in toluene the aliphatic hydrogen atoms are affected by the proximity of the phenyl group; because of resonance less energy is required for the separation of an aliphatic hydrogen atom; hence the activation energy should be lower.

The bromination of acetic acid proceeds readily, whereas much difficulty is encountered in brominating trimethylacetic acid. Experiments conducted in this Laboratory indicate that the bromination of propionic and *n*-butyric acid is photochemical and oxygen–catalyzed, whereas the bromination of acetic acid is little affected by light and oxygen. Obviously, the bromination of acetic acid proceeds by a mechanism different from that involved in bromination of other aliphatic acids.[8]

The formation of trimethylacetoxytrimethylacetic acid at elevated temperatures (150°) suggests that this product is formed according to the reaction

$$(6)\quad (CH_3)_3CCOOH + Br_2 \longrightarrow CH_2Br\text{-}C(CH_3)_2COOH + HBr$$

$$(7)\quad (CH_3)_3CCOOH + CH_2BrC(CH_3)_2COOH \longrightarrow (CH_3)_3CCOOCH_2C(CH_3)_2COOH + HBr$$

Experimental Part

The neopentane used in this work was prepared by the method of Whitmore and Fleming.[9] The final fractionation was kindly performed by the Universal Oil Products Company. A Raman spectral examination made by Dr. Rosenbaum of this Laboratory disclosed the presence of small amounts of unsaturated material. Further purification was effected by adding 1% of bromine to the neopentane in a bomb tube which was then sealed off in the presence of air. The tube was now placed about one centimeter from a mercury arc which warmed its contents to approximately 80°. Additions of 1% of bromine were continued until the color disappeared very slowly and uniformly. The product was then allowed to distill through wash towers filled, respectively, with concentrated sulfuric acid and 50% potassium hydroxide. It was finally passed through a tube containing calcium chloride. Fractionation gave two portions boiling between 9.4–9.5°; they had identical physical properties: $n^{0}{}_D$ 1.3515, m. p. −15.9°.

t-Butylbenzene was obtained from Dr. H. C. Brown.[10] It was distilled prior to use; $n^{20}{}_D$ 1.4925; b. p. 166.5–166.8° at 730 mm.

Trimethylacetic acid was prepared according to Sandborn and Bousquet.[11] It was distilled prior to use; b. p. 66–68° at 10 mm.; m. p. 34.5–35.0°.

The bromine used was of purified analytical grade.[12]

The apparatus used was similar to that previously employed for the bromination of cyclopropane.[12] However, instead of weighing the bromine sample, 0.064 ± 0.001 g. of bromine was delivered from a gas-measuring bulb maintained at 25°. The neopentane was distilled into a small tank which was attached to the vacuum line by a brass to glass ground joint. For each experiment, the gas was collected in a small tube calibrated (at 0°) to deliver 1.227 g. of neopentane. The resulting mole fraction of bromine in neopentane was 0.0223.

For the dark reaction, the tubes were placed in pipes and kept in a thermostat at the proper temperature, whereas, for the light reaction, the liquid phase was exposed to a 500-watt incandescent lamp at a distance of 10 cm. The extent of reaction was determined within an accuracy of 5% by comparison with color standards. Trimethylacetic acid (0.0196 mole) or *t*-butylbenzene (0.0172 mole) was added to the bomb tubes before they were sealed to the line. Where large concentrations of bromine were used, the bromine was measured directly into the reaction tube.

Trimethylacetoxytrimethylacetic Acid.—A mixture consisting of 26 g. of trimethylacetic acid and 20 g. of bromine was heated to 150° in a bomb tube in the dark. When the bromine color disappeared, the tube was cooled in liquid nitrogen and then opened. Hydrogen bromide and carbon dioxide were allowed to boil off, and the residue was made alkaline with aqueous alkali. The water-insoluble material was removed with ether. The aqueous portion was then acidified and extracted with ether. The ethereal extract was dried over calcium chloride and distilled. After removal of the ether and unreacted trimethylacetic acid, 2 g. of material boiling at 180–185° at 25 mm. was collected; this substance crystallized on standing. When recrystallized from ligroin, it formed long needles which showed parallel extinction and melted at 73.5°.

Anal. Calcd. for $C_{10}H_{18}O_4$: C, 59.35; H, 9.00; neut. equiv., 202; sapn. equiv., 202. Found: C, 58.72; H, 9.19; neut. equiv., 202.5; sapn. equiv., 196.

Hydrolysis of the material and micro distillation gave one fraction which was identified as trimethylacetic acid. It melted at 34° and did not lower the melting point of a known sample of trimethylacetic acid. The other fraction was hydroxytrimethylacetic. It crystallized in needles from ether–ligroin mixture and melted at 123–124° (reported m. p. 125°). Its neutral equivalent was 120 (calcd. 118). Its acetyl derivative melted at 55° (reported m. p. 56°).

---

[7] Hass, McBee and Weber, *Ind. Eng. Chem.*, **28**, 333 (1936).

[8] Kharasch and Hobbs, unpublished work.

[9] Whitmore and Fleming, THIS JOURNAL, **55**, 3803 (1933).

[10] Kharasch and Brown, *ibid.*, **61**, 2146 (1939).

[11] "Organic Syntheses," Collective Vol. I, p. 512.

[12] Kharasch, Fineman and Mayo, THIS JOURNAL, **61**, 2139 (1939).

Summary

1. In the absence of oxygen, bromine does not react with neopentane at 80°.
2. Oxygen has little effect on the reaction of bromine with neopentane at room temperature. At 80° it causes a slow reaction.
3. At 50° organic peroxides have an effect on the bromination of neopentane similar to that of oxygen at 80°.
4. The bromination of *t*-butylbenzene is exclusively nuclear.
5. When treated with bromine at 150° trimethylacetic acid yields brominated hydrocarbons and 9% of trimethylacetoxytrimethylacetic acid.

CHICAGO, ILLINOIS RECEIVED MAY 29, 1941

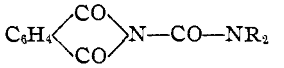
[CONTRIBUTION FROM THE COLLEGE OF PHARMACY, UNIVERSITY OF MICHIGAN]

Acid Amides as Hypnotics. III. Disubstituted Acetamides

BY F. F. BLICKE AND M. F. ZIENTY[1,2]

Di- and trisubstituted barbituric acids and, to a lesser extent, acyl- and alkylureas have been the subjects of numerous publications because of the favorable properties of many of their representatives as hypnotics. Disubstituted acetamides, on the other hand, have received relatively little attention. This paper represents a continuation of our study[3] of the last-mentioned type of product and describes a number of disubstituted acetamides in which one substituent is alkyl or arylalkyl and the other alkoxyalkyl or aryloxyalkyl.

In addition to the acetamides, three derivatives of phthalimide, namely, dimethyl-, diethyl- and dibutylcarbamylphthalimide were prepared; these products are inactive as hypnotics.



$$C_6H_4\langle{}^{CO}_{CO}\rangle N—CO—NR_2$$

We are indebted to Mr. J. W. Nelson and Dr. G. F. Cartland of The Upjohn Company for preliminary pharmacological evaluation of our products (Table II). The compounds, suspended in 5% acacia solution, were injected intraperitoneally into albino rats.

Experimental Part

The disubstituted diethyl malonates were prepared in the usual manner from the monosubstituted esters. Compounds 1, 2, 3, 4, 5, 7 and 16 (Table 1) were obtained by the use of diethyl ethylmalonate[4]; compounds 9, 10, 11, 12, 14 and 17 from diethyl β-phenylethylmalonate[5]; compound 13 from diethyl phenylmalonate[6]; compound 15 from diethyl γ-phenoxypropylmalonate[7] and compound 6 from diethyl β-benzyloxyethylmalonate.[8]

It was discovered that the use of powdered glass is distinctly advantageous in the preparation of a diethyl arylmalonate. For example, after the conversion of 1 mole of ethyl oxalate and 1.06 moles of ethyl phenylacetate into ethyl ethoxalylacetate, the addition of 40 g. of powdered glass reduced the time required for the elimination of carbon monoxide, and the formation of diethyl phenylmalonate, from five to six hours to two to three hours.

The disubstituted malonic acids, prepared by hydrolysis of the esters with alcoholic potassium hydroxide, were obtained initially as oils. Some of these crystallized rapidly, others only after a number of days.

The malonic acids were heated, in 15-g. portions, for fifteen minutes at 180° and then for one-half hour at 160°; the disubstituted acetic acids produced were distilled and converted into the acid chlorides with the aid of thionyl chloride.

The anomalous behavior of some of the acids, when heated with thionyl chloride, already has been described.[9]

The disubstituted acetamides were obtained when the acid chlorides were dropped, slowly, into an excess of strong ammonia water which was well cooled and stirred.

β-(β'-Methoxyethoxy)-ethyl Chloride.—To 700 g. (5.8 moles) of thionyl chloride which had been placed in a 3-l., three-necked flask, fitted with a stirrer and dropping funnel, and cooled well in a mixture of salt and ice, there was added a mixture of 63 g. (0.8 mole) of pyridine and 516 g. of β-(β'-methoxyethoxy)-ethyl alcohol[10] at such a rate that the temperature in the flask did not rise above 10°. After all of the material had been added, the flask was removed from the cooling-bath and the mixture stirred for two hours. After the addition of 100 cc. of water to dissolve the precipitated pyridine hydrochloride, the oily layer of the chloride was separated and dried with calcium chloride; b. p. 95-97° (59 mm.)[11]; yield 53%.

---

[1] This paper represents part of a dissertation submitted to the Horace H. Rackham School of Graduate Studies by M. F. Zienty in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the University of Michigan.

[2] The Upjohn Company Fellow.

[3] Blicke and Centolella, THIS JOURNAL, **60**, 2924 (1938).

[4] Fischer and Dilthey, *Ann.*, **335**, 334 (1904).

[5] Dolique, *Ann. chim.*, [10] **15**, 447 (1931).

[6] "Organic Syntheses," Vol. 16, p. 34.

[7] Carther, THIS JOURNAL, **50**, 1968 (1928).

[8] Bennett and Hock, *J. Chem. Soc.*, 475 (1927).

[9] Blicke, Wright and Zienty, THIS JOURNAL, **63**, 2488 (1941).

[10] This alcohol, methyl "carbitol," was purchased from the Carbide and Carbon Chemicals Corporation; "carbitol" and butyl "carbitol" were obtained from the same source.

[11] Cretcher and Pittenger (THIS JOURNAL, **47**, 164 (1925)), found 169° (744 mm.).