Rearrangement of 4-Chloro-3-heptanone.—A stirred suspension of 73.5 g. of sodium methylate in 400 ml. of dry ether below 10° was treated during one hour and 15 minutes with 200 g. of 4-chloro-3-heptanone. The solution was then refluxed for 40 minutes when 200 ml. of water was added to dissolve the salts. The organic layer was separated, combined with two ethereal extracts of the aqueous layer and dried over anhydrous sodium sulfate. The ether was removed by distillation and the residue fractionated yielding 147.3 g. (76.8%) of the methyl ester of 2-ethylvaleric acid, b.p. 79–80° (55 mm.), $n^{20}D$ 1.4080. Saponification of the ester yielded methyl alcohol as identified by its 3,5-dinitrobenzoate. The acid was liberated, separated and converted to the chloride thence to the amide. Melting point and mixed melting point with an authentic sample of the amide of 2-ethylvaleric acid was 100–101°. Another sample of the acid chloride was converted to the *p*-toluide. Melting point and mixed melting point with an authentic sample of the *p*-toluide of 2-ethylvaleric acid was 128–129°.

Rearrangement of 2-Chloro-3-heptanone.—The residue from the rearrangement of 112.5 g. after treatment as described above yielded 70.3 (64.5%) of the methyl ester of 2-ethylvaleric acid. Saponification of this ester yielded methyl alcohol identified by its 3,5-dinitrobenzoate. The amide was prepared from the liberated acid; melting point and mixed m.p. of this derivative with an authentic sample of the amide of 2-ethylvaleric acid was 100–101°. The *p*-toluide was also prepared. Melting point and mixed m.p. of this derivative with an authentic sample of the *p*-toluide of 2-ethylvaleric acid was 128–129°.

Chlorination of 3-Heptanone.—Chlorine gas (140 g.) was added to 225 g. of 3-heptanone below 5°. Nitrogen gas was then bubbled through the solution for 4.5 hours. The residue was fractionated through a column of about 30 theoretical plates yielding 161.2 g. (54.7%) of the monochloro derivative of 3-heptanone, b.p. 70° (17 mm.), $n^{20}D$ 1.4351.

Anal. Calcd. for $C_7H_{13}OCl$: Cl, 23.86. Found: Cl, 24.13, 24.22, 24.26.

A warming curve was run on 30 ml. of this sample and of a mixture of 30 ml. of this compound with 5 ml. of 2-chloro-3-heptanone. The liquidus points on both systems are tabulated.

Chlorinated product	
Liquidus point, °K.	217.43
2-Chloro-3-heptanone, %	(found from diagram) 74.0
Chlorinated product with 5 ml. 2-chloro-3-heptanone added to 30 ml.	
Liquidus point, °K.	218.50
2-Chloro-3-heptanone, %	found (from diagram) 77.8
	calcd. (from diagram) 77.8

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α-Halo Ketones. V. The Preparation, Metathesis and Rearrangement of Certain α-Bromoketones

BY ABRAHAM A. SACKS[1] AND J. G. ASTON

Certain bromoketones have been treated with sodium alcoholates to give esters in good yields. The bromo compounds from isopropyl propyl, isopropyl isobutyl and isopropyl neopentyl ketones give an ester corresponding to the bromine being removed from the α-carbon of the group other than isopropyl but, on hydrolysis, yield the hydroxyketone corresponding to the bromine being removed from the isopropyl group. The remainder behave "normally."

Further studies of the action of aqueous sodium hydroxide and of sodium methylate on certain α-bromoketones have been made. The results are reported in the present paper.

The α-bromoketone obtained from bromination of isopropyl isobutyl ketone gives an 80% yield of the methyl ester of diisopropylacetic acid by the reaction of sodium methoxide on its ether solution. If the bromoketone be treated with sodium hydroxide the product is α-hydroxyisopropyl isobutyl ketone as proved by oxidation to acetone and isovaleric acid.

Assuming direct replacement this indicates that the bromoketone is α-bromoisopropyl isobutyl ketone and that ester formation corresponds to a rearrangement from I to V in the scheme previously outlined.[2,3]

Since isobutyroin is oxidized to diisobutyryl, there is no doubt as to its structure. By the action of PBr_3, isopropyl α-hydroxyisobutyl ketone (VII in the above scheme) is converted into an α-bromoketone. If no rearrangement occurs, this bromoketone is isopropyl α-bromoisobutyl ketone (II in the above scheme) and for the present this doubtful assumption will be made.

Experimentally, this bromoketone does not lower the melting point of that derived from isopropy isobutyl ketone by direct bromination. However, in view of the fact that the bromoketone may be a mixture of the two bromoketones which could form compounds or solid solution, this fact is of little significance. The fact that it also gives methyl diisopropylacetate by the action of sodium methylate is, of course, no proof of identity. On hydrolysis, naturally, it gives α-hydroxyisopropyl isobutyl ketone (VI in the above scheme) which is not in conflict with the assigned structure.

Thus, it is possible that the bromoketone obtained by bromination of isopropyl isobutyl ketone is isopropyl α-bromoisobutyl ketone and corresponds to II in the above scheme. This is, of course, in violation of the "rules" for bromination of ketones.[4] However, these rules were based on a structure proof which disregarded rearrangements such as occur in going from II to VI.

There is another reaction which has a bearing on this point, namely, the action of nitrous acid on ketones in acid media, the conditions being not unlike those of bromination.[5]

In a series of ketones with isopropyl as the common group and the other group methyl, ethyl, propyl, *n*-butyl and isobutyl, respectively, substitution occurs exclusively on the α-carbon of the isopropyl group only when the other group is methyl. Thus,

(1) Abraham A. Sacks died suddenly on December 18, 1943. This paper was written from his thesis material.

(2) J. G. Aston and J. D. Newkirk, THIS JOURNAL, **73**, 3900 (1951).

(3) McPhee and Klingsberg, *ibid.*, **66**, 1132 (1944).

(4) Favorski, *J. prakt. Chem.*, [2] **88**, 641 (1913).

(5) Aston and Mayberry, THIS JOURNAL, **57**, 1888 (1935).

it is possible that the bromination product of isobutyl isopropyl ketone is also a mixture of the two α-bromoketones.

The following conclusions, therefore, are the only ones which can be drawn about the bromination of ketones. (a) Substitution of hydrogen on the α-carbon of any alkyl group is easier than that of methyl (deduced from the work of McPhee and Klingsberg as well as by analogy with the results of nitrosation). (b) There is no reason to conclude that substitution of hydrogen on the α-carbon of a secondary alkyl group is easier than that of a primary alkyl group (deduced from the above experiments and by analogy with the nitrosation experiments).

In addition to the isopropyl isobutyl ketone we have brominated, at room temperature without solvent, the series of ketones listed in Table I, each of which has a secondary alkyl group attached to the carbonyl. The yields, boiling range and bromine analysis of the bromo compounds are listed in Columns 2, 3, 4, 5 and 6. In none of the cases, with the possible exception of isopropyl isobutyl ketone, is there any reason for assigning any preference to either of the two α-carbon atoms for the location of the entering bromine.

TABLE I

YIELD AND PROPERTIES OF MONOBROMO KETONES

Ketone	Yield, %	Monobromo compound boiling range °C.	Mm.	Bromine, % Calcd.	Found
Isopropyl propyl	32.5	67–68	15	41.38	40.75
Diisopropyl	72	59–61	18–20	41.38	Crude
Isopropyl butyl	36	86–87	17	38.6	40.1
Isopropyl isobutyl (a)	45	77–78	16–17	38.6	38.15
Isopropyl *t*-butyl	77	65–66	13–14	38.6	38.9
Isopropyl amyl	31	99–101	19	36.1	37.1
Isopropyl neopentyl	76	85–86	19	36.1	36.26
s-Butyl propyl	40	76–79	17	38.6	...
3,5,5-Trimethylhexanone	55	93–94	16	36.1	36.2

Table II lists the percentage yield (Column 4), of esters (Column 3), obtained by treating an ether solution of the bromoketone (Column 1) with the anhydrous sodium alcoholate (Column 2). The boiling points, analyses of the ester (calculated and found) and refractive index are given in Columns 5, 6, 7, 8, 9, 10 and 11. Column 12 gives an index letter for later use in referring to each ester.

With one exception, the acid prepared from the esters has been identified by mixing melting point of a derivative with one prepared by a method which left no doubt concerning its structure.

The ester from the action of sodium methylate on the α-bromo derivative of isopropyl neopentyl ketone was only identified as methylisopropyl *t*-butyl acetate by elimination. The other possible product is methyl dimethylneopentylacetate. This latter ester was prepared from 3-bromo-3,5,5-trimethyl-2-hexanone. The corresponding acid and its derivatives were prepared from dimethylneopentylcarbinylmagnesium chloride.[6] All were quite different from the compounds from the α-bromo derivative of isopropyl neopentyl ketone. Nevertheless, the hydrolysis of the α-bromo derivative of isopropyl neopentyl ketone yields neopentyl α-hydroxyisopropyl ketone.

(6) Whitmore, Wheeler and Surmatis, THIS JOURNAL, **63**, 3237 (1941).

TABLE II

YIELDS OF ESTERS OBTAINED BY THE ACTION OF CERTAIN ANHYDROUS ALCOHOLATES ON CERTAIN BROMOKETONES

Bromo ketone derived from	Na alcoholate	Ester, acetate	Yield, %	B.p. of ester °C.	Mm.	Analyses of ester,[b] % Calcd. C	Calcd. H	Found C	Found H	$n^{25}D$	Index letter
Isopropyl propyl	Methylate	Methyl ethylisopropyl-	69	146–147	741	66.63	11.88	66.87	11.29	1.4082–1.4090	A
Diisopropyl	Isopropylate	Isopropyl dimethylisopropyl-	17	165–166.5	730	69.72	11.70	70.12	11.55	1.4111–1.4119	B
	Benzylate	Benzyl dimethylisopropyl-	29	139.14		76.32	9.15	75.81	9.29	1.4889	C
Isopropyl butyl	Methylate	Methyl dimethylbutyl-	73	64	18	68.31	11.47	68.5	11.07	1.4142	D
Isopropyl isobutyl	(a) Methylate[a]	Methyl diisopropyl-	84	79	40	68.31	11.47	69.06	11.58	1.4161–1.4165	E
	(b) Methylate[a]										
		Methyl diisopropyl-	83	78	40	68.31	11.47	68.93	11.66	1.4160–1.4163	F
Isopropyl amyl	Methylate	Methyl dimethylamyl-	83	79–80	17	69.72	11.70	70.10	11.61	1.4182–1.4189	G
Isopropyl neopentyl	Methylate	Methyl isopropyl-*t*-butyl-	93	56	10	69.72	11.70	70.20	11.67	1.4240	H
s-Butyl propyl	Isopropylate	Isopropyl methylethylpropyl-	41	75–78	17–19	70.92	11.91	71.08	11.81	1.415–1.418	I
3,5,5-Trimethyl-2-hexanone	Methylate	Methyl dimethylneopentyl-	78	65	15	...	...	...	...	1.4238	J

[a] The bromoderivative of isopropyl isobutyl ketone obtained by direct bromination is marked (a) while that obtained by the action of PBr_3 on isobutyroin is marked (b). As shown by mixed melting points, they are identical and both are probably α-bromoisobutyl isopropyl ketone. [b] These analyses were performed entirely by Arlington Laboratories, Fairfax, Virginia. Also, all the C, H and N, analyses reported in the text.

In the case of propyl isopropyl ketone the ester obtained from the monobrominated ketone also arises from migration of the secondary alkyl group. Here again the hydrolysis of the bromoketone yields the α-hydroxyisopropyl ketone. It is of interest to note that the action of sodium methylate on α-bromodiisopropyl ketone yielded α-methoxydiisopropyl ketone. The action of sodium isopropylate on α-bromoisopropyl *t*-butyl ketone gave no ester but only a small yield of material which was apparently α-isopropoxyisopropyl *t*-butyl ketone; on α-bromoisopropyl phenyl ketone it also gave no ester.

Experimental

Preparation of Ketones.—Diisopropyl ketone was obtained by fractionation of the commercial product. Isopropyl propyl ketone, diisopropyl ketone, isopropyl butyl ketone, isopropyl *t*-butyl ketone and isopropyl amyl ketone were prepared by oxidation of the corresponding carbinols from the action of the appropriate Grignard reagent on isobutyraldehyde. *s*-Butyl propyl ketone and 3,5,5-trimethyl-2-hexanone were prepared by the oxidation of the corresponding carbinols prepared, respectively, from butyraldehyde using *s*-butylmagnesium bromide and by the action of methylneopentylcarbinylmagnesium bromide on acetaldehyde. Isopropyl neopentyl ketone was prepared by the action of isopropylmagnesium bromide on methyl *t*-butylacetate.

Preparation of Bromoketones by Bromination.—The procedure was essentially the one used by Favorski.[4] An equivalent quantity of bromine was dropped slowly into the ketone (0.5–2.0 moles) while cooling with ice-water. Either carbon dioxide or nitrogen was passed through the solution to sweep out hydrogen bromide. The bromine was added slowly enough to maintain an amber color. Sometimes two drops of 30% hydrobromic acid was used to start the reaction and in some cases the ice-water cooling had to be dispensed with to maintain the right rate of reaction. The last of the hydrogen bromide was removed by pumping and shaking with anhydrous potassium carbonate and the product distilled in vacuum over 0.5 to 2.0 g. of fresh potassium carbonate.

Preparation of α-Bromoisobutyl Isopropyl Ketone (b) from Isobutyroin.—Seventy-two grams (0.5 mole) of isobutyroin was treated with 46 g. of PBr_3 (0.17 mole) at between 0 and 5° over 1.5 hours. After stirring overnight, with the ice-bath removed, water was added to the mixture and the bromoketone extracted with ether. After removing the ether from the extract and distilling through a column, 50.6 g. (0.24 mole or 48% yield) of bromoketone was obtained, b.p. 81.5–82.0 at 21 mm.

Melting Point of α-Bromoisobutyl Isopropyl Ketone (Samples (a) and (b)).—The sample was contained in a test-tube surrounded by a bath of ethyl acetate to which pieces of Dry Ice were added. While cooling the sample was stirred until completely frozen. The whole was then allowed to warm slowly with stirring and the temperature was observed on a pentane thermometer immersed in the sample. The melting points deduced from the warming curve were: *sample (a) from bromination of ketone*, −11 to −9.5°; *sample (b) from isobutyroin*, −11.5 to −10.5°; *60% (a) 40% (b)*, −11 to −10°.

Sodium Methylate and Solid Sodium Isopropylate.—The anhydrous alcohol was allowed to react completely with freshly cut sodium. The excess alcohol was then distilled off and the last traces removed under vacuum.

Reaction between Sodium Benzylate and α-Bromodiisopropyl Ketone.—Benzyl alcohol (0.87 mole) in dry ether (300 cc.) was treated with metallic sodium (0.87 mole) and the mixture refluxed for 75 hours. One hundred and fifty-four grams of α-bromodiisopropyl ketone (0.80 mole) was added to this directly over a period of three hours. After stirring 20 hours, water was added to dissolve the solid. Benzyl diisopropylacetate, as recorded in Table II, was obtained from the potassium carbonate dried ether layer by distillation.

Action of Sodium Methylate and Isopropylate on the Bromoketones.—To a suspension of the alcohol-free sodium alcoholate in dry ether (about 300 cc. per mole) was added slowly, with stirring, the bromoketone (about 0.7 mole per mole of sodium alcoholate) diluted with an equal volume of dry ether. After stirring till reaction was complete (about 20 hours) enough water was added to dissolve the sodium bromide and excess sodium alcoholate. The ether layer was separated and the aqueous layer ether extracted. The ether layer, combined with the extracts, was dried over anhydrous potassium carbonate and fractionated through a column. The boiling point yields and analyses of the esters are given in Table II. The amounts of bromoketone used varied from 0.24 to 1.0 mole.

Identification of Esters (A) Methyl Ethylisopropylacetate.—Six grams of ester (0.042 mole) was refluxed with 50 cc. of 25% sodium hydroxide until all the ester had dissolved: 3.8 g. of acid (0.029 mole, 69% yield) was obtained, b.p. 108–109.5° at 20 mm., $n^{20}D$ 1.4211. Calcd. for $C_7H_{14}O_2$: neut. equiv., 130.2. Found: neut. equiv., 130.9.

By the action of 10 g. of thionyl chloride on 2.4 g. of acid (0.018 mole), obtained in the same way, 2.2 g. of acid chloride (0.015 mole, 83% yield) was obtained, b.p. 51–52° at 18 mm. which was added to 2.8 g. of aniline in 100 cc. of dry ether. The anilide was crystallized twice from ligroin and twice from aqueous methyl alcohol, m.p. 119.5–120.5°. In the same way, this same anilide (m.p. 121.2–122.2°) was obtained from ethylisopropylacetic acid which had been prepared by treating ethyl ethylmalonate with isopropyl iodide.[7] The mixed melting points of the anilides was 120–121.5°.

Similarly the α-naphthalides were prepared. The one from the rearranged product melted at 149–151° after several crystallizations from aqueous methyl alcohol, while the one from the product of the malonic ester synthesis melted at 150.7–152.2°. The mixed melting point was 150–152°.

(B and C) Isopropyl and Benzyl Dimethylisopropylacetates.—Eight and eight-tenths grams (0.05 mole) of the isopropyl ester was cleaved by refluxing with 50 cc. of constant boiling hydriodic acid for ten hours to yield 0.7 g. (0.005 mole, 10% yield) of an acid melting at 50 to 51°.[8] Similarly from 8.0 g. (0.036 mole) of the benzyl ester was obtained 2.0 g. (0.015 mole, 42% yield) of an acid melting between 48.5 and 50° which was shown to be identical with the free acid from the isopropyl ester by mixed melting point. (Calcd. for $C_7H_{14}O_2$: neut. equiv., 130.2. Found: neut. equiv., 130.7.)

The acid was converted into the acid chloride (b.p. 52° at 20 mm.) in 77% yield and thence to an amide (m.p. 130–131°),[9] and anilide (m.p. 78–79° after crystallization from ligroin). This anilide did not depress the melting point (78–79°) of an anilide prepared by the action of dimethylisopropylcarbinylmagnesium chloride on phenylisocyanate.

(D) Methyl Dimethylbutylacetate.—This ester may have contained another ester as an impurity, perhaps methyl propylisopropylacetate. By refluxing for 15 hours with constant boiling hydriodic acid, a 62% yield of acid was obtained, b.p. 107–108 at 12 mm.[10] This acid was converted into the acid chloride, b.p. 77–82 at 31 mm.,[11] in 81% yield with thionyl chloride and then into an amide (m.p. 92.5–93.5°) and an anilide (m.p. 70–76°) which could not be further purified either by crystallization from ligroin or aqueous methyl alcohol. The amide gave a mixed m.p. of 92.5–93.5° with an authentic sample of dimethylbutylacetamide, m.p. 92.8–93.8.[12] An anilide prepared from *n*-butyldimethylcarbinylmagnesium chloride and phenyl isocyanate melted 88–89°. Mixed with the above anilide the melting point was 73–86°. In view of the melting point of the anilide and the lower boiling point of the acid than observed by Meerwein[10] (120–122° at 16 mm.) it is doubtful if this acid was pure.

The ester could be almost completely saponified by refluxing with 25% sodium hydroxide for 15 hours.

(7) Crossley and LeSueur, *J. Chem. Soc.*, **77**, 91 (1900), who give 114–115° as the melting point of ethylisopropylacetanilide.

(8) Richard, *Ann. chim. phys.*, [8] **21**, 353 (1910), gives 50° as the melting point of dimethylisopropylacetic acid.

(9) Locquin and Leers, *Compt. rend.*, **179**, 55 (1924), give 129° as the melting point of dimethylisopropylacetamide.

(10) Meerwein, *Ann.*, **419**, 149 (1919), gives b.p. 120–122° at 16 mm. for dimethylbutylacetic acid.

(11) Locquin and Leers, *Compt. rend.*, **178**, 2095 (1924).

(12) Leers, *Bull. soc. chim.*, [4] **39**, 651 (1926), gives m.p. 92° for dimethylbutylacetamide but gives b.p. of 117–119° at 12 mm. for the acid.

(E and F) Methyl Diisopropylacetate.—The ester (E) from the action of sodium methylate on the product from the bromination of isopropyl isobutyl ketone was refluxed with constant boiling hydriodic acid for 12 hours to give a 72% yield of the acid (b.p. 110–111° at 15 mm., $n^{20}D$ 1.4269. Calcd. for $C_8H_{16}O_2$: neut. equiv., 144.2. Found: neut. equiv., 145.7); which was converted through the acid chloride (b.p. 68–70° at 20 mm., 80% yield) to the amide (m.p. 147–147.8°) and the anilide (m.p. 146.5–147.5°). The identity of this anilide was established by a mixed melting point (146.5–147.5°) with one prepared in the same way from the acid obtained (m.p. 146.5–147°) from ethyl cyanoacetate and isopropyl iodide.

The methyl ester was only slightly hydrolyzed after 60 hours of refluxing with 25% potassium hydroxide.

Similarly from the ester (F) was obtained an 89% yield of the acid (b.p. 124–124.5° at 26 mm., $n^{20}D$ 1.4268) which, with thionyl chloride, gave an acid chloride in 57% yield (b.p. 75–78° at 28 mm.) and an anilide m.p. 146.5–147.5°, mixed m.p. with the anilide from ethyl cyanoacetate synthesis 146.5–147.5°.

(G) Methyl Dimethylamylacetate.—The ester was refluxed for 7.5 hours with constant boiling hydriodic acid to give an acid (b.p. 145–145.5° at 32 mm., $n^{20}D$ 1.4298) in 45% yield, which was converted by thionyl chloride to an acid chloride (b.p. 94.5–96.5° at 30 mm.) in 80% yield and an anilide (m.p. 91.5–92° from aqueous methyl alcohol).[13] A mixed melting point with a known sample of dimethylamylacetamide (m.p. 102.5–103.5°) was 101.5–103°. A mixed melting point with the anilide (m.p. 91.5–92° from ligroin) prepared by the action of dimethylamylcarbinylmagnesium chloride on phenyl isocyanate was 91 to 92°. The ester was hydrolyzed to the acid in 75% yield by refluxing for 12 hours with 25% sodium hydroxide.

(H) Methyl Isopropyl-*t*-butylacetate.—The ester was not appreciably hydrolyzed after 75 hours of boiling with 25% sodium hydroxide, but was cleaved by refluxing with constant boiling hydriodic acid for 16 hours to give an acid in 45% yield (b.p. 122.5–123.8° at 22 mm., $n^{20}D$ 1.4343. Calcd. for $C_9H_{18}O_2$: neut. equiv., 158.2. Found: neut. equiv., 159.3). The acid was converted by thionyl chloride into an acid chloride (b.p. 68–74° at 20 mm.) in 84% yield. *Anal.* Calcd. for $C_9H_{17}OCl$: Cl, 20.07. Found: Cl, 20.3. The anilide prepared from this acid chloride melted 173.5 to 174.5°. *Anal.* Calcd. for $C_{15}H_{23}ON$: N, 6.0. Found: N, 6.5.

A semicarbazone of the acetonyl ester (m.p. 174–175°) was prepared by heating the sodium salt with monochloroacetone for one hour at 115°, extracting the ketone derivative with ether and converting into the semicarbazone after removing the ether. *Anal.* Calcd. for $C_{13}H_{25}O_3N_3$: N, 15.49. Found: N, 15.72. For dimethylneopentylacetic acid the anilide has been found to melt at 77.5–78°[5] and the semicarbazone of the acetonyl ester at 155°.[14]

(I) Isopropyl Methylethylpropylacetate.—The ester was not appreciably saponified on refluxing for 100 hours with 25% sodium hydroxide. It was cleaved by refluxing with constant boiling hydriodic acid for 15 hours to give the acid in 30% yield (b.p. 125.5–126.5° at 23 mm.; calcd. for $C_8H_{16}O_2$: neut. equiv., 144.2. Found: neut. equiv., 145.3).

The α-aminonaphthalide prepared from the acid chloride (b.p. 73–75° at 23 mm., 70% yield) melted at 120.8 to 122° after six recrystallizations from aqueous methyl alcohol. The same α-aminonaphthalide (m.p. 120.5–122°) was obtained by the action of methylethylpropylcarbinylmagnesium chloride on α-naphthylisocyanate. The mixed melting point was 120.5–122°.

(J) Methyl Dimethylneopentylacetate.—The acid (m.p. 46–47°) was obtained in 70% yield by refluxing with constant boiling hydriodic acid for 15 hours. The acid was identified by a mixed melting point (45.5 to 47°) with the known acid (m.p. 45.5 to 46.5°). The latter was prepared by the oxidation of triisobutylene.[15] It was identified by the mixed melting point of the amide and anilide[15] with the corresponding derivatives of an acid proved, by mixed melting point, to be identical with one prepared by treating dimethylneopentylcarbinylmagnesium chloride with carbon dioxide.[6]

The ester could be saponified completely by refluxing with 25% sodium hydroxide for 12 hours.

Hydrolysis and Oxidation of the α-Bromo Derivative of Isopropyl Isobutyl Ketone.—Seven grams (0.034 mole) of bromoketone (a) obtained by brominating isopropyl isobutyl ketone, was refluxed with 75 cc. of 20% sodium hydroxide for 20 hours and the mixture steam distilled. The ether extract of the steam distillate on fractionation yielded 2.1 g. (0.014 mole, 43% yield) of hydroxy ketone (b.p. 79–83° at 24 mm., $n^{20}D$ 1.4251–1.4256). As will be seen below, this compound was not isobutyroin and hence was α-hydroxyisopropyl isobutyl ketone.

One and a half grams (0.01 mole) of this material was treated with 1 g. of potassium dichromate in 45 cc. of water and 1 cc. of concentrated sulfuric acid for 4 hours at 80–90°. After being made alkaline, the reaction mixture was distilled through a column. Half of a gram of distillate boiling between 54 and 60° was obtained corresponding to an 85% yield of acetone. This gave 0.8 g. (0.003 mole) of dibenzalacetone (m.p. 111.5–112.5°) corresponding to a 30% yield of acetone based on the material oxidized. The identity of this material was verified by a mixed melting point.

The residue was acidified and the organic acid removed by steam distillation. The acid was converted, through the acid chloride, into the anilide (m.p. 109.5–110.5°). This was identified as isovaleranilide by mixed melting point.

The hydrolysis of 7.5 g. of the bromoketone (b) from the action of PBr_3 on isobutyroin was carried out in a similar manner except 100 cc. of 6% sodium hydroxide was used. The product was the same (b.p. 83–85° at 28 mm., $n^{20}D$ 1.4252, 60% yield) and gave practically identical results on oxidation with dilute potassium dichromate.

The oxidation of isobutyroin ($n^{20}D$ 1.4272) with dilute potassium dichromate in the manner described above gave no acetone or acid but apparently only diisobutyril.

Hydrolysis and Oxidation of the α-Bromo Derivative of Isopropyl Neopentyl Ketone.—Thirty-three grams (0.15 mole) of bromoketone was hydrolyzed by refluxing with 0.16 mole of sodium hydroxide in 100 cc. of water for 12 hours. The hydroxyketone (11.9 g., 0.075 mole, 50% yield, b.p. 101 at 50 mm., $n^{20}D$ 1.4362–1.4368) was ether extracted and separated by fractional distillation.

The hydroxy ketone (4 g., 0.025 mole) was oxidized with 2.4 g. of potassium dichromate in 100 cc. of water, acidified with 2 cc. of concentrated sulfuric acid, by heating for 6 hours at 75–80°. The 0.4 g. of acetone (0.0083 mole, 33% yield), obtained by distilling the reaction mixture through a column, was converted into 0.51 g. of dibenzalacetone (m.p. 111.5–112.5°, 0.0002 mole, 8% yield based on the hydroxy ketone) which was identified by mixed melting point.

A distillation carried out with 0.025 mole of acetone dissolved in an aqueous solution identical with that used in oxidizing the hydroxy ketone yielded substantially the same amounts of acetone.

The *t*-butylacetic acid obtained by ether extraction of the residue from the distillation weighed 0.8 g. (0.0069 mole, 28% yield, b.p. 87–88° at 17 mm., $n^{20}D$ 1.4120). It was converted to the amide (m.p. 129.5–131°) which was identified by mixed melting point (130–131°) with a known sample.[16]

Hydrolysis and Oxidation of the α-Bromo Derivative of Isopropyl Propyl Ketone.—Thirteen grams (0.067 mole) was hydrolyzed with 100 cc. of 7% sodium hydroxide solution. By ether extraction 5.9 g. (0.045 mole, 68% yield) of product (b.p. 70–73°, $n^{20}D$ 1.4230–1.4242) was obtained. Oxidation of 1.3 g. (0.01 mole) of this material gave 0.7 g. (0.003 mole, 30% yield) of dibenzalacetone.

α-Methoxydiisopropyl Ketone.—To 0.87 g. of anhydrous alcohol-free sodium methylate in 300 cc. of dry ether was added over two hours, 154 g. (0.8 mole) of α-bromodiisopropyl ketone dissolved in an equal volume of dry ether. After stirring for 20 hours, the reaction mixture was hydrolyzed; the ether layer was separated, combined with two extracts of the aqueous layer and dried with anhydrous potassium carbonate. Fractionation of this layer yielded 80.3 g. (0.62 mole, 77% yield) of liquid, b.p. 149–151° at 732 mm., $n^{20}D$ 1.4113–1.4120.

(13) Leers, ref. 12, gives 101–102° for the melting point of dimethylbutylacetamide.

(14) C. D. Wilson, Ph.D. Thesis, The Pennsylvania State College, 1939 (with F. C. Whitmore).

(15) Miner, Ph.D. Thesis, The Pennsylvania State College, 1940 (with F. C. Whitmore).

(16) Homeyer, Whitmore and Wallingford, THIS JOURNAL, **55**, 4209 (1933), give the melting point of the amide as 132°.

Anal. Calcd. for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.83; H, 11.07. The compound did not give an acid when cleaved with constant boiling hydriodic acid, but gave a 2,4-dinitrophenylhydrazone, m.p. 173–174° after recrystallization from methyl alcohol.

Anal. Calcd. for $C_{14}H_{21}O_5N_4$: N, 17.22. Found: N, 16.90.

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Preparation and Properties of Serum and Plasma Proteins. XXX. Crystalline Derivatives of Human Serum Albumin and of Certain Other Proteins[1a,b]

BY J. LEWIN[1c]

A systematic study has been made of the crystallization of several proteins under conditions in which a wide variety of ions or neutral molecules may be incorporated into the crystals. The reagents employed included multivalent anions and cations, many containing elements of high atomic number, and also several dyes and drugs. Crystals have been obtained of over 200 derivatives of the mercury dimer of human serum mercaptalbumin, and also of many derivatives of human decanol albumin and bovine serum albumin, together with a few derivatives of the metal-binding β-globulin of plasma. For any given added salt, dye or drug, crystals of the protein derivative could be obtained when the molar ratio of added reagent to protein was varied over a wide range. Such crystals containing ions of heavy metals should provide useful material for X-ray studies. The composition of albumin crystals containing complex ions of platinum has been studied as a function of the composition of the solution from which they are crystallized. For this purpose a new micro method of platinum analysis has been developed, which makes use of the ultraviolet absorption of the chloroplatinate ion.

Introduction

Combinations of proteins with ions of heavy metals have been known for more than a century.[2] It has been widely believed that such ions act primarily as denaturing agents. However, it is now becoming clear that complexes of native proteins with the ions of heavy metals can be formed under carefully controlled conditions, and that the native protein can be regenerated from these complexes. For example, Michael[3] has studied combinations between complex chromium compounds and several proteins; Perlmann[4] has studied metaphosphate binding and has crystallized a metaphosphoric derivative of egg albumin; and Lewin, Baudouin and Hillion[5,6,7] have prepared triiodomercuric (HgI_3^-) derivatives of a number of proteins. The amounts of these anions fixed by the proteins could be varied systematically up to a maximum equivalent to the number of free cationic groups in the protein molecule. As the number of bound groups approached this maximum, the complexes became very insoluble.

In the studies reported here, the range of compounds studied for their ability to form complexes with proteins has been greatly widened. The number of moles of added reagent per mole of protein was generally between one and ten, occasionally more. In this range the complexes of the proteins studied were very soluble in water, but crystallization of the protein salts could readily be achieved at low temperature by addition of methanol or ethanol. The method derives from that developed by Cohn, Hughes, and others for the fractionation of plasma and tissue proteins, and for the crystallization of some of the pure proteins obtained.[8,9,10,11] The added reagents, from which crystalline derivatives were prepared, include simple and complex inorganic compounds, and various organic compounds including a number of dyes and drugs.

Materials

Proteins.—As already stated, four kinds of protein preparations were used during this work. They are in order of increasing frequency of use: (1) crystalline human metal-combining serum β_1-globulin. The sample was prepared by Dr. K. Schmid following the procedure of B. A. Koechlin[10]; (2) crystalline bovine albumin[11] prepared in the Armour Laboratories; (3) human serum albumin crystallized from high ethanol concentration and ionic strengths in the range 0.05–0.3 in the presence of decanol[11]; and (4) the crystalline mercury dimer of mercaptalbumin, obtained from Fraction V of human plasma by the procedure of Hughes.[9,12]

The simple inorganic reagents employed were prepared from commercial Baker or Merck C.P. products. The

(1) (a) This paper is Number 92 in the series "Studies on the Plasma Proteins" from blood collected by the American Red Cross, on products developed by the University Laboratory of Physical Chemistry Related to Medicine and Public Health, Harvard University. (b) This work was supported by the Eugene Higgins Trust, by grants from the Rockefeller Foundation, the National Institutes of Health, by contributions from industry, and by funds of Harvard University. (c) Research Fellow of the French Government Cultural Relations Committee, 1946–1947; present address: Centre National de Transfusion Sanguine, 6 Rue Alexandre-Cabanel, Paris XV, France.

(2) For the early literature see, for instance, G. Mann, "Chemistry of the Proteins," The Macmillan Co., London and New York, 1906; and F. N. Schulz, "Die Grösse des Eiweissmoleküls," Jena, 1908. Other more recent studies are discussed in the "The Chemistry of Amino Acids and Proteins," edited by C. L. A. Schmidt, C. C. Thomas, Springfield, Illinois, 2nd Edition, 1944.

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(12) W. L. Hughes, Jr., *Cold Spring Harbor Symposia*, **14**, 79 (1950). This protein, according to Hughes, is a dimer of mercaptalbumin (the fraction of serum albumin containing a single free SH-group per molecule) in which two mercaptalbumin residues are linked through their –SH groups, by a mercury atom. It can be formulated Alb.S–Hg–S–Alb, where Alb.S– represents the mercaptalbumin residue