NOTES

Alicyclic Diamines. Polyadipamides of Bis-(4-aminocyclohexyl)-methane

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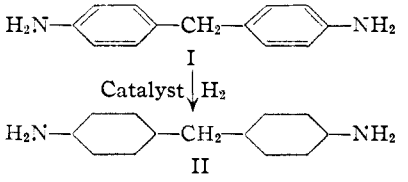
Hydrogenation of bis-(4-aminophenyl)-methane (I) yields bis-(4-aminocyclohexyl)-methane (II).



The bis-(4-aminocyclohexyl)-methane is obtained as mixtures of the three geometric isomers, namely, the *cis–cis*, *cis–trans* and *trans–trans* configurations.[1] Under various hydrogenation conditions[2] mixtures of bis-(4-aminocyclohexyl)-methane are obtained which vary in the proportions of the three isomers present. An estimate of the relative amounts can be obtained by isolation of the individual isomers, methods for which have been described.[1]

Configuration of the diamine isomers plays an important role in determining the properties of the polyamides prepared therefrom. Investigation of representative polyadipamides was undertaken to elucidate this situation.

Discussion

The adipic acid polyamides of the individual pure isomers and of known mixtures of the isomers exhibited considerable differences in melting point. In light transmission the polymers ranged from glass-like clarity to opacity. Polymer properties for a particular isomer mixture have been readily reproduced. The results for various compositions are given in Table I.

Table I

Polyadipamides of Bis-(4-aminocyclohexyl)-methane

Isomer composition of diamine, %			Light transmission	Softening temp., °C.
c–c	*c–t*	*t–t*		
..	97.5	2.5	Transparent	253
..	95.2	4.8	Opaque	261
15.0	77.9	7.1	Transparent	277
30.0	57.9	12.1	Transparent	255
52.4	28.2	19.4	Transparent	244
73.7	..	26.3	Transparent	257
15.0	75.3	9.7	Translucent	260
30.0	55.5	14.5	Translucent	259
52.1	25.6	22.3	Translucent	262
30.1	50.5	19.4	Opaque	>300
15.0	70.5	14.5	Opaque	>300

The polyamide from adipic acid and the *trans–trans* diamine isomer is highly crystalline, opaque and infusible below its decomposition temperature (about 310°). The polyamide from the *cis–trans* isomer is transparent, crystalline and orientable as determined by X-ray diffraction, and softens at about 252°. The polyamide from the *cis–cis* isomer is transparent, amorphous, and not readily orientable. It softens at about 253°.

Adipic acid polyamides were prepared from two-component mixtures of the pure isomers. All the polyamides from mixtures of the *cis–trans* and *cis–cis* isomers were transparent and softened between 244 and 260°. Increased crystallinity and orientability were noted as the proportion of the *cis–trans* isomer was increased. Polyadipamides of mixtures of *cis–cis* and *trans–trans* isomers with up to 26% of the latter were transparent and fusible. Polyamides from mixtures of the *cis–trans* and *trans–trans* isomers with more than 2.5% of the latter were opaque.

In three-component systems quantities of the *trans–trans* isomer between 2.5 and 26%, depending on the proportion of the *cis–trans* and *cis–cis* isomers, also gave transparent, fusible polyamides. Further increasing the concentration of the *trans–trans* isomer by about 8% gave opaque, higher melting polyadipamides. The polyamides with appreciably larger proportions of *trans–trans* isomer have been infusible below 300° and opaque.

In general, isomer mixtures obtained by hydrogenation which were liquid at 25° gave fusible, transparent polyadipamides while solid mixtures of diamine isomers gave opaque polymers. Short catalyst contact time and low temperature are conditions for hydrogenating bis-(4-aminophenyl)-methane that apparently favor conversion into a preponderance of the *cis–cis* and *cis–trans* isomers.[1,2] This has been realized with bis-(4-aminocyclohexyl)-methane prepared batchwise over ruthenium catalysts at about 100°, and in continuous flow hydrogenation over ruthenium catalysts at about 140–150°. The adipic acid polyamides from bis-(4-aminocyclohexyl)-methane prepared under these conditions have been readily fusible and transparent. Hydrogenation at moderately increased temperatures or appreciably longer contact times has resulted in increased proportions of the *trans–trans* isomers as evidenced by the nature of the adipic acid polyamide which was fusible but opaque. Hydrogenation batchwise at 150° or under continuous flow at temperatures above 160° resulted in further increases in the *trans–trans* isomer content, as inferred from the infusibility and opacity of the adipic acid polyamides.

Experimental

Preparation of Adipic Acid Salts of Bis-(4-aminocyclohexyl)-methane.—The preparation of the adipic acid salts of the diamine isomers is exemplified by the procedure employed for the preparation of the *trans–trans* salt. To a solution of 50.37 g. (0.239 mole) of the *trans–trans* isomer in 290 ml. of absolute ethanol was added all at once a warm solution of 34.82 g. (0.238 mole, 0.42 mole per cent. less than the equivalent amount) of recrystallized adipic acid in

(1) A. E. Barkdoll, H. W. Gray and W. Kirk, Jr., This Journal, **73**, 741 (1951).

(2) A. E. Barkdoll, D. C. England, H. W. Gray, W. Kirk, Jr., and G. M. Whitman, *ibid.*, **75**, 1156 (1953).

175 ml. of absolute ethanol, an additional 20 ml. of absolute ethanol being used for rinsing. The salt precipitated instantly with incipient boiling of the solution. The hot mixture was stirred thoroughly to ensure homogeneity and was stored at 6° for 2 days. The microcrystalline salt was collected by suction filtration, washed with 20 ml. of absolute ethanol and dried under reduced pressure at 60–80° for several days to remove alcohol, which was held very tenaciously.

Somewhat less ethanol was employed for formation of the adipic acid salts of the other two isomers. The *cis–trans* salt precipitated as tiny, oily spheres that crystallized rapidly on scratching. The diamine samples were weighed in a nitrogen-filled dry-box to prevent absorption of carbon dioxide and water during handling. Polonium-plated gold foil was employed to dissipate the static charges acquired by the diamines during handling. The inflection points for the three salts were in the *p*H range of 7.53–7.58, as determined by electrometric titration of 0.5% aqueous solutions.

Preparation of Polyamides.—Polymer preparations were carried out in Pyrex brand glass tubes 28 × 180 mm. o.d. with a wall thickness of 2 mm. to which were sealed necks 11 × 220 mm. o.d. About 10 g. of salts was polymerized in each run. Mixtures of salts of the different isomers were stirred to assure that the resulting polyamide would be homogeneous. The tube containing the salt was evacuated and filled with oxygen-free nitrogen three times at atmospheric pressure, and then evacuated to a pressure of 5 mm. and sealed. The sealed tube was heated for one hour at 210° in a lead-bath. The tube was then cooled and opened and the contents heated under oxygen-free nitrogen at 1 atm. pressure for one-half hour at 306° (benzophenone vapor bath). Heating was continued for 1.5 hours at 285° (diphenylene oxide vapor bath) without allowing the molten polymer to cool appreciably while changing the bath.

Characterization of Polyamides.—Inherent viscosities[3] were predominantly in the range 0.72–1.05 which indicated that high molecular weight was attained. Polymer melting points were determined in air on a copper block.

(3) Determined with 0.5 g. of polymer in 100 ml. of *m*-cresol at 25°; *cf.* L. H. Cragg, *J. Colloid Sci.*, **1**, 261 (1946).

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Some Reactions of Cinnamoylpyridinium Chloride

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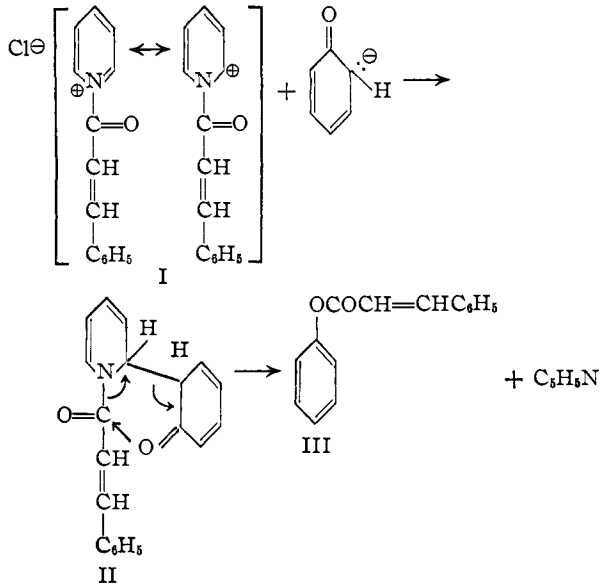
In the course of another investigation we had cause to examine the chemical behavior of cinnamoylpyridinium chloride (I) and, in view of the recent interest[1,2,3,4] in compounds of the same general type as I, we are reporting our results at this time. The reaction of cinnamoyl chloride and pyridine in dry ethereal solution at or slightly below room temperature gave I in essentially quantitative yield as a white solid of rather indefinite melting point. The compound was a powerful acylating agent, reacting with water[1] or dilute solutions of bases[5] to give cinnamic anhydride in 13–71% yield depending on the conditions of the experiment. Acylation of ethyl benzoylacetate with I gave ethyl β-cinnamoyloxycrotonate in 59% yield. The reaction of pyridine, benzoyl chloride and dimethylaniline at room temperature for seven weeks or at 100° for six days has been reported to give 4-(*p*-dimethylaminophenyl)-pyridine in 22–27% yield.[4,6] The latter was obtained in 35% yield (along with traces of cinnamaldehyde) from the reaction of I and dimethylaniline in pyridine at steam-bath temperatures for eight hours.

The most interesting cinnamoylation was that of phenol, for this reaction appeared to take place in two distinct steps. When I was mixed with phenol (in the presence or absence of pyridine) a bright yellow substance formed which slowly and completely disappeared as crystals of colorless phenyl cinnamate deposited (73–83% yield). 2,6-Dimethylphenol behaved in the same fashion, giving 76% of 2,6-dimethylphenyl cinnamate. If the colored substance may be assumed to be a true intermediate, its formation may be rationalized by assuming a mechanism for the reaction similar to that proposed by Doering and McEwen[2] for several reactions of benzoylpyridinium chloride.[7] Thus, I which has an electron deficiency at the α- and γ-positions, reacts with the electron-donating keto form of the phenoxide ion to give the colored complex II,[8] which is converted *via* the quasi six-membered ring to the ester III.



Experimental[9]

Cinnamoylpyridinium Chloride (I).—To a solution of 83.5 g. (0.5 mole) of cinnamoyl chloride (prepared in 95% yield from cinnamic acid and 1.5 moles of thionyl chloride, b.p. 133–134° (15 mm.)) in 200 ml. of dry ether was added slowly with cooling 60 g. (0.76 mole) of pyridine dissolved in 100 ml. of dry ether. The mixture was allowed to stand 30 minutes (protected from moisture) and was filtered, washed with cold ether and dried over potassium hydroxide *in vacuo*. The yield of cinnamoylpyridinium chloride was 113–122 g. (92–98%), m.p. about 122–124°. The compound decomposed when distilled under reduced pressure. The com-

(1) H. Adkins and Q. E. Thompson, THIS JOURNAL, **71**, 2242 (1949).
(2) W. von E. Doering and W. E. McEwen, *ibid.*, **73**, 2104 (1951).
(3) Q. E. Thompson, *ibid.*, **73**, 5841 (1951).
(4) W. E. McEwen, E. H. Terss and I. W. Elliott, *ibid.*, **74**, 3605 (1952).
(5) E. Wedekind, *Ber.*, **34**, 2070 (1901).
(6) For the original report of this reaction see: E. Koenigs and E. Ruppelt, *Ann.*, **509**, 142 (1934).
(7) See footnote 4 of ref. 2. Apparently Adkins and Thompson[1] have succeeded in isolating benzoylpyridinium chloride (although not in analytically pure form) as well as numerous other aroylpyridinium chlorides.
(8) Intermediate II may be in equilibrium with a similar substance in which the cyclohexadienone unit is in the γ-position (see ref. 2).
(9) Melting points are corrected, boiling points are not. Analyses were by Clark Microanalytical Laboratory, Urbana, Illinois, unless otherwise noted.

pound was also prepared using dry petroleum ether or dry benzene as the reaction medium.

Anal. Calcd. for $C_{14}H_{12}NOCl$: Cl, 15.17. Found: (analysis by author) Cl, 14.85.

Some preparations gave products (usually pale yellow or off-white in color) that were obviously not pure, but these were found to be satisfactory for synthetic use. All of the reactions cited below were run with the solid cinnamoylpyridinium chloride and most of them were run also by adding the calculated amount of cinnamoyl chloride and pyridine to the other reactants. The yields were comparable by both procedures.

Cinnamic Anhydride.—To a solution of 2 ml. of water in 70 ml. of acetone was added 15 g. (0.06 mole) of cinnamoylpyridinium chloride. The mixture was stirred vigorously for five minutes and poured into 500 ml. of water containing 5 ml. of hydrochloric acid. The solid was filtered off, washed with 5% sodium bicarbonate and with water. The air-dried product was recrystallized from absolute ethanol, giving 6.0 g. (71%) of cinnamic anhydride, m.p. 135–136°. When the procedure of Wedekind[5] was followed, the yield of cinnamic anhydride was 13% (after recrystallization). The principal product whenever a large excess of water was used (as in the Wedekind procedure) was cinnamic acid.

Ethyl β-Cinnamoyloxycrotonate.—A mixture of 24.6 g. (0.1 mole) of cinamoylpyridinium chloride and 19.2 g. (0.1 mole) of ethyl benzoylacetate was warmed on the steam-bath for two hours and allowed to stand overnight. The crude mixture was washed with 5% hydrochloric acid, water, 5% sodium bicarbonate and water in that order. The solid remaining was recrystallized from absolute ethanol, giving 19 g. (59%) of ethyl β-cinnamoyloxycrotonate, m.p. 125.4–126.1°. The product gave no enolic tests.

Anal. Calcd. for $C_{20}H_{18}O_4$: C, 74.52; H, 5.63. Found: C, 74.30; H, 5.39.

4-(*p*-Dimethylaminophenyl)-pyridine.—A mixture of 12.3 g. (0.05 mole) of cinnamoylpyridinium chloride, 4.0 g. (0.05 mole) of pyridine and 6.0 g. (0.05 mole) of dimethylaniline was heated on the steam-bath for eight hours. The mushy mixture was made acid with concentrated hydrochloric acid and steam distilled. The 150-ml. of steam distillate was extracted with ether, the ether evaporated and the residue treated with phenylhydrazine in ethanol,[10] giving *ca.* 0.1 g. of cinnamaldehyde phenylhydrazone, m.p. 167–168°. The residue from the distillation was filtered from a large mass of black tarry material and the filtrate was made alkaline. Steam distillation of the alkaline mixture yielded 3.0 g. (50%) of dimethylaniline. The residue in the distillation flask was filtered off and recrystallized three times from 9:1 ethanol:chloroform to give 3.5 g. (35%) of 4-(*p*-dimethylaminophenyl)-pyridine, m.p. 234–235°, as colorless, flat plates which colored quickly in air to a light yellow solid. This interesting substance had, as one might expect, indicator properties, being yellow in acidic (organic or inorganic) and colorless in neutral or alkaline solutions. It reacted (in chloroform solution) with acid halides to give brilliantly colored complexes, *e.g.*, a bright red with benzoyl chloride and a deeper red with cinnamoyl chloride, even in high dilutions.

Phenyl Cinnamate.—To 24.5 g. (0.1 mole) of cinnamoylpyridinium chloride was added 9.4 g. (0.1 mole) of phenol. A bright yellow color appeared immediately and slowly faded on standing. From this point two procedures were used: (a) 16.0 g. (0.2 moles) of pyridine was added and the mixture was heated for four hours on the steam-bath or (b) the mixture (without added pyridine) was allowed to stand at room temperature overnight. In each case the resultant mixture was poured into 500 ml. of water and stirred until the oily lower layer solidified. The solid was collected on the buchner funnel, washed with 10% hydrochloric acid, 5% sodium bicarbonate, 10% potassium hydroxide, and with water in that order, and recrystallized from 95% ethanol, giving 16–18.5 g. (73–83%) of phenyl cinnamate, m.p. 75–76°. This procedure compares favorably with respect to yields (reported 56–75%) and with respect to the manipulations required with that reported in reference 11.

(10) E. H. Huntress and S. P. Mulliken, "Identification of Pure Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1941, p. 72.

(11) *Org. Syntheses*, **20**, 77 (1940).

2,6-Dimethylphenyl Cinnamate.—To 24.5 g. (0.1 mole) of cinnamoylpyridinium chloride was added 12.2 g. (0.1 mole) of 2,6-dimethylphenol (DPI 1772). A bright yellow-orange color appeared briefly then disappeared. To the mixture was added 8.0 ml. of pyridine and it was allowed to stand overnight. The reaction mixture was worked up as described for phenyl cinnamate (above), giving 19 g. (76%) of 2,6-dimethylphenyl cinnamate, m.p. 91–92°.

Anal. Calcd. for $C_{17}H_{16}O_2$: C, 80.92; H, 6.39. Found: C, 81.39; H, 6.32.

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Reactions of 1,3-Diphenylisobenzofuran with Acetylenic Dienophiles

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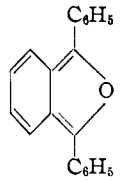
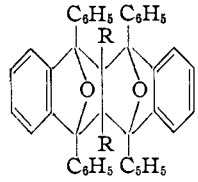
Although additions of 1,3-diphenylisobenzofuran (I) to a number of ethylenic dienophiles have been reported,[1–4] the literature does not seem to contain any examples of reactions of this interesting substance with acetylenic dienophiles. In connection with a separate study, we have had occasion to carry out such reactions. The preparation and properties of the adducts and their derivatives are reported here.

The reaction of I with acetylenedicarboxylic acid (II) produced the bis-adduct (III) in near-quantitative yield. Even in the presence of a large excess of II, only III could be isolated, albeit in smaller yield.

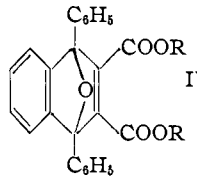


I



III, R = COOH

Diene addition of I to ethyl acetylenedicarboxylate afforded a 1:1 adduct (IVa) in excellent yield. The ester (IVa) was readily reduced to the



IV a, R = C_2H_5
b, R = H

corresponding dihydro adduct (V). Saponification of IVa yielded the very unstable unsaturated acid IVb, isolated only as the monohydrate. This acid suffers partial retrograde diene addition in alkaline solution and consequently, the saponification of the ester (IVa) yielded a small quantity of I, identified as the autoxidation product, *o*-dibenzoylbenzene. Pyrolysis of IVb at the melting point (140°) resulted in virtually quantitative conversion to the bis-adduct (III), presumably by retrograde diene addition and recombination of the addends. The facile dissociation of V and especially of IVb

(1) R. Weiss, A. Abeles and E. Knapp, *Monatsh.*, **61**, 162 (1932).

(2) E. de B. Barnett, *J. Chem. Soc.*, 1326 (1935).

(3) C. Dufraisse and R. Priou, *Bull. soc. chim.*, [5] **5**, 502 (1938).

(4) A. Etienne and A. Spire, *Compt. rend.*, **230**, 2030 (1950).

parallels the previously reported[2,3] behavior of other adducts of I.

Experimental[5]

Reaction of 1,3-Diphenylisobenzofuran with Acetylenedicarboxylic Acid.—A solution of 0.61 g. of I[6,7] and 0.30 g. of II in 5 cc. of benzene and 5 cc. of ether was heated at reflux for 5 minutes. The ether was allowed to distil out of the reaction mixture and the residual solution was boiled an additional 55 minutes. After this time, the characteristic blue-green fluorescence of the isobenzofuran was no longer visible, even in ultraviolet light. The solution was concentrated by distillation and treated with a little carbon tetrachloride. The bis-adduct (III) crystallized as tiny, white prisms, m.p. 195.5–198.5°. The yield was 0.74 g. (quantitative). The analytical sample, recrystallized from benzene–carbon tetrachloride, had m.p. 203.5–204°.

Anal. Calcd. for $C_{24}H_{16}O_5$ (1:1 adduct): C, 74.99; H, 4.20. Calcd. for $C_{44}H_{30}O_6$ (bis-adduct): C, 80.72; H, 4.62. Found: C, 80.82, 80.54; H, 4.88, 5.00.

When the reaction was carried out under similar conditions using a 9:1 ratio of II to I, only III was isolated. The yield was 50%.

Reaction of 1,3-Diphenylisobenzofuran with Ethyl Acetylenedicarboxylate.—A solution of 0.54 g. of I and 0.34 g. of ethyl acetylenedicarboxylate in 4 cc. of benzene was heated at reflux for 105 minutes. The solvent was evaporated and the residue crystallized from benzene–ethanol to yield 0.74 g. (84%) of IVa, m.p. 139–140°. Recrystallization from benzene–ethanol raised the melting point to 143.0–143.5°. The substance instantaneously decolorized potassium permanganate in acetone at room temperature.

Anal. Calcd. for $C_{28}H_{24}O_5$: C, 76.35; H, 5.49. Found: C, 75.98; H, 5.18.

Catalytic Reduction of IVa.—A solution of 0.60 g. of IVa in 20.cc. of ethyl acetate was added to a suspension of Adams catalyst (previously generated from 0.05 g. of platinic oxide) in 10 cc. of ethyl acetate. The reaction mixture was stirred in hydrogen at one atmosphere pressure. The theoretical quantity of gas was absorbed in 38 minutes, whereupon the catalyst was filtered off and the filtrate evaporated to a thick oil which exhibited an intense blue-green fluorescence. The oil crystallized readily upon trituration and the product was recrystallized from ethanol to yield 0.40 g. of the dihydroester as white, rhombohedral tablets, m.p. 131.5–133°. After several recrystallizations from ethanol, the m.p. remained constant at 137.5–138°. A mixed m.p. with IVa was depressed to 106–120°. The dihydroester apparently suffers retrograde diene addition upon fusion, for the melt of the pure substance shows the characteristic blue-green fluorescence of I.

Anal. Calcd. for $C_{28}H_{26}O_5$: C, 76.00; H, 5.92. Found: C, 76.26; H, 6.07.

Saponification of IVa.—A mixture of 0.64 g. of IVa and 0.64 g. of potassium hydroxide in 10 cc. of ethanol was heated at reflux. The reaction mixture immediately turned bright-yellow and became strongly fluorescent. After 2.5 hours, the mixture was diluted with water and extracted with several portions of chloroform until the chloroform layer was no longer fluorescent. The chloroform solution was washed with water, dried over sodium sulfate and evaporated. The residue was recrystallized from benzene–Skellysolve B to give 0.03 g. of crude *o*-dibenzoylbenzene, m.p. 140–147° alone or mixed with an authentic sample.[6]

The original alkaline solution was acidified with concentrated hydrochloric acid and extracted with ether. The ether extract, after having been washed with water and dried over sodium sulfate, was evaporated to a thick, pale-yellow oil which crystallized readily from benzene–Skellysolve B as 0.30 g. (54%) of IVb, m.p. 134.5–135° with decomposition. Recrystallization from a mixture of ethyl acetate, benzene and Skellysolve B afforded pure-white rosettes of sharply-defined, transparent staves. The acid decomposed sharply at 139° with violent frothing when heated slowly from room temperature. When the substance was inserted into a bath preheated to 140.5° and the temperature was raised very slowly (1° per minute), decomposition occurred at 144.5–145°.

The acid was readily soluble in neutral ethanol. When this colorless solution was treated with a few drops of 10% sodium hydroxide, it immediately turned yellow and showed a blue-green fluorescence.

Freshly-purified samples of the acid were pure-white in the solid state. The crystals became yellow in about two hours when dried at 1 mm. at room temperature. The dried material showed essentially the same melting point characteristics as the freshly-recrystallized substance.

Anal. Calcd. for $C_{24}H_{16}O_5 \cdot H_2O$: C, 71.63; H, 4.51. Found (after drying at 56° and 1 mm. for 2 hours, then at room temperature for 48 hours over phosphorus pentoxide): C, 71.34; H, 4.10. Found (after drying at 56° and 1 mm. for 24 hours, then at room temperature for 1 week over phosphorus pentoxide): C, 71.47; H, 4.70.

Pyrolysis of IVb.—Eighteen-hundredths of a gram of finely-powdered IVb was carefully heated to its melting point in a slow current of nitrogen. The exit gases were passed into baryta. At 140° the solid frothed vigorously and a sudden surge of gas produced a voluminous precipitate in the baryta solution. The melt was kept at 140–143° for 15 minutes and then allowed to cool. The yellow-brown glassy residue was dissolved in ether and extracted with potassium carbonate solution. The aqueous layer was freed of a small quantity of insoluble material by filtration and then acidified with concentrated hydrochloric acid. The precipitated solid, after drying at the pump, weighed 0.12 g. Recrystallization from benzene–Skellysolve B afforded glittering, short needles or prisms, m.p. 204–205°, alone or mixed with a sample of III prepared by diene addition.

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(5) Melting points are corrected. The microanalyses are by Mr. Joseph Pirie of this Laboratory and by Dr. Adalbert Elek, Elek Microanalytical Laboratory.

(6) R. Adams and M. H. Gold, THIS JOURNAL, **62**, 56 (1940).

(7) The preparation of I by the procedure of reference 6 was found to be superior to that of A. Guyot and J. Catel, *Bull. soc. chim.*, **35**, 1124 (1906). Compare E. Bergmann, *J. Chem. Soc.*, 1147 (1938).

Preparation of *p*-Acetaminobenzaldehyde Thiosemicarbazone

BY A. DAS AND S. L. MUKHERJEE

RECEIVED AUGUST 13, 1952

Domagk, *et al.*,[1] reported the activity of thiosemicarbazones against tuberculosis. Of the two most effective thiosemicarbazones, *p*-acetaminobenzaldehyde thiosemicarbazone known commercially as TB/I and the *p*-ethylsulfonyl derivative known as TB/III, the former has found more popularity with the medical profession. This compound has been synthesized in a variety of ways[2,3,4] by using thiosemicarbazide in all cases. In still another method[5a] hydrazinium thiocyanate has reacted with aromatic aldehydes to give appropriate thiosemicarbazones. Almost simultaneously the preparation of acetone thiosemicarbazone by using hydrazinium thiocyanate with acetone has been reported by Sunner.[5b]

Following the well-known extension of Wöhler's synthesis as applied in the above two methods[5a,5b] as well as in the preparation of thiosemicarbazide[6]

(1) Domagk, *et al.*, *Naturwissenschaften*, **33**, 315 (1946).

(2) Domagk (to I. G. Farbenindustrie), *German Patent Appli.*, **176**, 219 (1943); *Ind. Eng. Chem.*, **42**,1868 (1950).

(3) "Manufacture of thiosemicarbazone derivative of acetylamino or amino substituted aromatic aldehyde," Indian Patent 43,527 dated 22nd July 1950.

(4) Wilheim, *Acta Univ. Szeged, Chem. Phys.*, **3**, 54 (1950); *C. A.*, **46**, 2521 (1952).

(5) (a) Puetzer, *et al.*, THIS JOURNAL, **73**, 2958 (1951); (b) Sunner, *C. A.*, **45**, 5486 (1951).

(6) Freund and Wischewiansky, *Ber.*, **26**, 2877 (1893).

the present investigation was undertaken to see whether a thiosemicarbazone can be successfully developed from a hydrazone which can be prepared from an excess of hydrazine hydrate and an aldehyde. *p*-Acetaminobenzaldehyde thiosemicarbazone has thus been prepared by allowing *p*-acetaminobenzaldehyde hydrazone to react with ammonium thiocyanate.

Further attempts to prepare it *in situ* from a mixture of *p*-acetaminobenzaldehyde, excess hydrazine sulfate and ammonium thiocyanate in water also resulted in the formation of thiosemicarbazone in excellent yield. The reaction in this case proceeds through the formation of azine which is converted into its hydrazone in the presence of excess of hydrazine. This with thiocyanate gives the thiosemicarbazone after subsequent rearrangement of the thiocyanate derivative as

$$\underset{\text{aldehyde}}{RCHO} + \underset{\text{hydrazine}}{NH_2NH_2} \longrightarrow \underset{\text{azine}}{RCH{=}NN{=}CHR} \longrightarrow$$

$$\underset{\text{hydrazone}}{RCH{=}H{-}NH_2} \longrightarrow \underset{\text{thiocyanate}}{RCH{=}N{-}NH_2HSCN} \longrightarrow$$

$$R = CH_3CONHC_6H_4- \qquad \underset{\text{thiosemicarbazone}}{RCH{=}N{-}NH{-}\overset{\overset{S}{\|}}{C}{-}NH_2}$$

Experimental

***p*-Acetaminobenzaldehyde.**—The *p*-aminobenzaldehyde (Beard and Hodgson[7]) was acetylated in chloroform with acetic anhydride. It recrystallized from hot water in pale yellow needles, m.p. 158°.[8]

***p*-Acetaminobenzaldehyde Hydrazone.**—*p*-Acetaminobenzaldehyde (7 g.) was refluxed with 75% hydrazine hydrate (20 cc.) in alcohol (40 cc.) for one hour. The clear solution was allowed to cool when colorless crystalline needles of hydrazone separated, m.p. 165–166°.

Anal. Calcd. for $C_9H_{11}N_3O$: N, 23.7. Found: N, 23.6.

It is of interest to note that when *p*-acetaminobenzalazine is heated with hydrazine hydrate in alcohol *p*-acetaminobenzaldehyde hydrazone is formed which when heated with water changes itself to *p*-acetaminobenzalazine, m.p. 315–316° as confirmed by a mixed m.p. with an authentic sample prepared by the method of Bernstein, *et al.*[9]

***p*-Acetaminobenzaldehyde Thiosemicarbazone.**—(i) The hydrazone was suspended in water and acidified to congo red with concd. hydrochloric acid. Ammonium thiocyanate (15 g.) was then added and the mixture concentrated on a water-bath. Water was added and concentrated as before. This process was repeated until the residue was crystalline. It was then filtered and washed with hot water. Yellow crystals were obtained having m.p. 225–226° (dec.). There was no depression of m.p. when mixed with a sample prepared from the aldehyde and thiosemicarbazide; Bernstein, *et al.*,[9] reported a m.p. 223–224° (dec.).

Anal. Calcd. for $C_{10}H_{12}N_4OS$: N, 23.7. Found: N, 23.5.

This identification was confirmed by deacetylating when *p*-aminobenzaldehyde thiosemicarbazone was obtained m.p. 196° with no depression of m.p. with an authentic sample (Berstein, *et al.*).

(ii) To *p*-acetaminobenzaldehyde (8 g.) in alcohol (50 cc.) was added a 300-cc. solution of a mixture of hydrazine sulfate (20 g.) and sodium carbonate (8 g.) when an instantaneous precipitate[10] was formed. To this mixture was added ammonium thiocyanate (16 g.) in water (100 cc.) and the mixture heated under a reflux for 11 hours until the frothing completely subsided. The large flat crystals of *p*-acetaminobenzaldehyde thiosemicarbazone were collected; yield (8 g.) m.p. 226–227° (dec.) confirmed by a mixed m.p. with the above specimen.

Anal. Calcd. for $C_{10}H_{12}N_4OS$: N, 23.7. Found: N, 23.6.

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(7) Beard and Hodgson, *J. Chem. Soc.*, 4 (1944).

(8) Friedlander and Cohn, *Monatsh.*, **24**, 1, 87 (1903), reported a m.p. 161°.

(9) Bernstein, *et al.*, THIS JOURNAL, **73**, 906 (1951).

(10) Identified as the *p*-acetaminobenzalazine, m.p. 315-316° with no depression on mixed m.p. with an authentic sample. *Anal.* Calcd. for $C_{18}H_{18}N_4O_2$: N, 8.69. Found: N, 8.48.

Preparation and Properties of Pure Ammonium DL-Lactate[1]

BY E. J. COSTELLO AND E. M. FILACHIONE

RECEIVED OCTOBER 31, 1952

Ammonium lactate, which can readily be prepared by fermentation of carbohydrates in the presence of ammonia[2–4] is potentially an important primary fermentation product. Previous studies at this Laboratory have shown that ammonium lactate upon interaction with alcohols produces lactic ester and ammonia in high yields.[5–7] However, comparatively little information about the physical properties of ammonium lactate has been reported,[8–11] only the distillation of ammonium lactate in vacuum[10] and certain properties of aqueous ammonium lactate[11] having been recorded. Pure crystalline ammonium lactate, however, was not used in these investigations, and lactamide was most likely a contaminant.[12] This paper reports the preparation of pure crystalline ammonium lactate and the determination of various properties of this pure salt.

Experimental

Preparation of Ammonium Lactate.—The equivalence point of ammonium lactate was first determined as follows: An approximately 0.1 *N* lactic acid solution was prepared by diluting a high quality 20% lactic acid solution and refluxing for one day to completely remove any polylactic acid. A 25-cc. aliquot of this solution (0.098 *N*) was titrated potentiometrically with freshly standardized ammonium hydroxide (0.102 *N*). The change in *p*H in the vicinity of the equivalence point was pronounced, considerably more than in the titration of a weaker acid such as acetic acid. The equivalence point for ammonium lactate corresponded to a *p*H of 6.65.

The 80% edible grade DL-lactic acid of commerce (4 kg.) was diluted to approximately 20% concentration with water (12 kg.) and this diluted solution was heated under a reflux condenser for 24 hours at 85–90°. Thus the polylactic acid, present in concentrated lactic acid solutions, was almost completely hydrolyzed to lactic acid. The equilibrated 20% aqueous lactic acid solution was then neutralized with concentrated ammonium hydroxide to a *p*H of 7.0. The dilute ammonium lactate solution was concentrated

(1) Article not copyrighted.

(2) H. C. Jansen, Dutch Patent 57,848 (July 15, 1946).

(3) L. H. C. Perquin, Dutch Patent 58,545 (Nov. 15, 1946).

(4) L. L. Kempe, H. O. Halvorson and E. L. Piret, *Ind. Eng. Chem.*, **42**, 1852 (1950).

(5) E. M. Filachione, E. J. Costello and C. H. Fisher, THIS JOURNAL, **73**, 5265 (1951).

(6) E. M. Filachione and E. J. Costello, *Ind. Eng. Chem.*, **44**, 2189 (1952).

(7) E. M. Filachione and C. H. Fisher, U. S. Patent 2,565,487 (Aug. 28, 1951).

(8) B. E. Brown and F. R. Reid, *Am. Fertilizer*, **95**, No. 12, 12 (1941).

(9) F. Groebe and O. Spengler, German Patent 680,660 (Aug. 17, 1939).

(10) R. Escales and H. Koepke, *J. prakt. Chem.*, **87**, 258 (1913).

(11) A. A. Dietz, E. F. Degering and H. H. Schopmeyer, *Ind. Eng. Chem.*, **33**, 1444 (1941).

(12) J. Wislicenus, *Ann.*, **133**, 257 (1865).

TABLE I

PHYSICAL PROPERTIES OF AQUEOUS AMMONIUM LACTATE

Concn., % by wt.	$n^{20}D$	$n^{25}D$	$n^{40}D$	d^{20}_4	d^{25}_4	d^{40}_4	Viscosity, cps. 20°	25°	40°
0.0	1.3330	1.3321			0.9971		1.01	0.8	
5.0	1.3407	1.3400	1.3383	1.0132	1.0155	1.0066	1.18	1.04	0.86
15.0	1.3576	1.3557	1.3540	1.0412	1.0385	1.0346	1.53	1.35	0.97
28.8	1.3786	1.3775	1.3756	1.0810	1.0788	1.0730	2.66	2.17	1.60
46.4	1.4064	1.4050	1.4037	1.1288	1.1249	1.1198	6.28	5.22	3.36
70.0	1.4416	1.4406	1.4379	1.1826	1.1808	1.1729	43.05	32.87	16.35
78.8	1.4543	1.4536	1.4503	1.2006	1.1984	1.1904	160.64	115.0	46.31

in a steam-heated laboratory-size glass circulating evaporator[13] operated at 30 mm. Because of the explosion hazard[14] resulting from mercury exposed to ammonia, the pressure was initially adjusted to 30 mm.; the manometer then was closed from the system and the pressure periodically checked by momentarily opening the mercury manometer to the system. The solution was evaporated until its temperature reached 70°. The concentrated ammonium lactate solution was then withdrawn from the evaporator, and the *p*H, which was approximately 6, was adjusted to 6.7 by addition of concentrated ammonium hydroxide. Analysis of the solution by the formol titration method[15] showed an ammonium lactate content of 84.5%. Analysis of the solution for total nitrogen[16] and for ammonia nitrogen by the magnesium oxide method[17] showed 11.1 and 11.0% nitrogen, respectively; thus the salt was essentially free of lactamide.

Crystalline Ammonium Lactate.—To 100 g. of 84.5% aqueous ammonium lactate was added 250 ml. of benzene and the stirred mixture was refluxed for 3.5 hours (pot temp., 79–85°) with continuous removal of water; a water separating trap was employed to separate water from its benzene azeotrope. Benzene was then evaporated in vacuum from the reaction mixture and the resulting sirupy liquid was stored in a refrigerator. Crystals slowly separated over a storage period of approximately one month and these were removed by filtration.

Once crystals were obtained it was more convenient to isolate the solid ammonium lactate as follows: 500 g. of 84.5% ammonium lactate solution was cooled in an ice-bath, after which seeds of crystalline ammonium lactate were added to the cooled solution. On filtration 268 g. (63% of the salt in solution) of crystalline ammonium lactate was collected.

At room temperature the crystalline salt was soluble in water, glycerol and 95% ethyl alcohol; slightly soluble in methanol; and insoluble in absolute ethyl, *n*-propyl, isopropyl and *n*-butyl alcohols, ether, acetone and ethyl acetate. With the exception of isopropyl alcohol, acetone and ether, the solid salt was soluble in these solvents at approximately their boiling temperatures. A saturated solution of ammonium lactate in water at 20°, analyzed by the formol titration method,[15] contained 224.7 g. of salt per 100 g. of water, corresponding to a 69.2% solution.

n-Propyl alcohol was found to be the best solvent for recrystallization of ammonium lactate. Two recrystallizations from *n*-propyl alcohol resulted in an anhydrous salt melting at 91–94°.

Anal. Calcd. for $C_3H_9O_3N$: NH_3, 15.90; lactic acid, 84.10. Found: NH_3, 15.78; lactic acid, 84.10.

Physical Properties of Aqueous Ammonium Lactate.—Solutions of various concentration were prepared by dissolving the pure crystalline salt in distilled water. The refractive index, density and viscosity were determined at 20, 25 and 40° by standard procedures. The results are shown in Table I.

Distillation of Ammonium Lactate.—Crystalline ammonium lactate, 51 g., was distilled in an alembic still[18] at 0.2 to 0.4 mm. and 38 g. of a colorless sirupy liquid was collected at 76.5 to 83°. (Care was taken as described above to prevent ammonia from contacting the mercury in the manometer.) In accordance with observations of previous investigators,[10] the distillate appeared to be a complex of equimolar amounts of ammonium lactate and lactic acid, $CH_3CHOHCO_2NH_4 \cdot CH_3CHOHCO_2H$. *Anal.* Calcd. for $C_6H_{15}O_6N$: N, 7.10; neut. equiv., 197.2. Found: N, 6.85; neut. equiv., 195.8. Formol titration showed an equivalent weight as an ammonium salt of 214 (theoretical value, 197.2).

The distillate was redistilled at various pressures in the range of 0.1 to 10 mm.; the following boiling points were observed: 74° at 0.14 mm., 89.5° at 0.50 mm., 99° at 0.75 mm., 102.5° at 1.00 mm., 130° at 4.20 mm., and 141° at 8.30 mm.

Preparation of Dibutylammonium Lactate from Ammonium Lactate.—A mixture of 74% aqueous ammonium lactate (1 mole) and di-*n*-butylamine (1 mole) was refluxed for two hours to remove ammonia. On cooling in the refrigerator, a solid crystallized from the reaction mixture. The solid was separated and recrystallized from benzene to give 116 g. (53% yield) of dibutylammonium lactate, m.p. 76.5–78°. No attempt was made to recover material in the mother liquors. When the material was mixed with an authentic sample of dibutylammonium lactate[19] the melting point was not depressed.

Hygroscopic Properties of Ammonium Lactate.—The apparatus designed by Wink[20] was used in a constant temperature room at 25 ± 2° to determine the hygroscopicity of ammonium lactate. The procedure was substantially that described for determination of the hygroscopicity of lactamide derivatives.[21] A 2- to 4-g. sample of the salt, weighed to the nearest 0.2 mg., was distributed on glass wool mats in the dishes of the Wink apparatus. The samples were exposed to atmospheres of various relative humidity and weighed daily until the composition changed less than 0.1% in 24 hours. This composition, usually attained in one to two weeks, was taken as the equilibrium value. Saturated solutions of the following salts, relative humidity at 25° indicated in parentheses, were used to provide constant humidity[20–23]: potassium acetate (22%), magnesium chloride hexahydrate (33%), potassium nitrite (48%), magnesium nitrate hexahydrate (52%), sodium bromide (58%), sodium nitrite (64%) and sodium chloride (75%). Zero humidity was obtained with anhydrous calcium sulfate. The results are summarized in Table II and Fig. 1. For comparison, the curve for glycerol[24] is included in Fig. 1. The absorption curve for ammonium lactate (ABCD, Fig. 1) was obtained by exposing the crystalline ammonium lactate to the various relative humidities. The desorption curve (DCA, Fig. 1) was obtained by transferring equilibrium composition samples to vessels of lower relative humidity. All the equilibrium composition samples corresponding to the points on curve DCA of Fig. 1 were liquid. The liquid samples obtained at relative humidities

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(14) J. J. Sampey, *Chem. Eng. News*, **25**, 2138 (1947).

(15) A. Ronchese, *J. pharm. chim.*, **25**, 611 (1907); *Analyst*, **32**, 303 (1907).

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(17) Association of Official Agricultural Chemists, "Official and Tentative Methods of Analysis," 6th ed., 2.29, p. 28, Washington, D. C., 1945.

(18) W. P. Ratchford and C. E. Rehberg, *Anal. Chem.*, **21**, 1417 (1949).

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(20) W. A. Wink, *Ind. Eng. Chem., Anal. Ed.*, **18**, 251 (1946).

(21) W. P. Ratchford, *Ind. Eng. Chem.*, **42**, 1565 (1950).

(22) D. S. Carr and B. L. Harris, *ibid.*, **41**, 2014 (1949).

(23) R. H. Stokes and R. A. Robinson, *ibid.*, **41**, 2013 (1949).

(24) W. C. Griffin, *ibid.*, **37**, 1126 (1945).

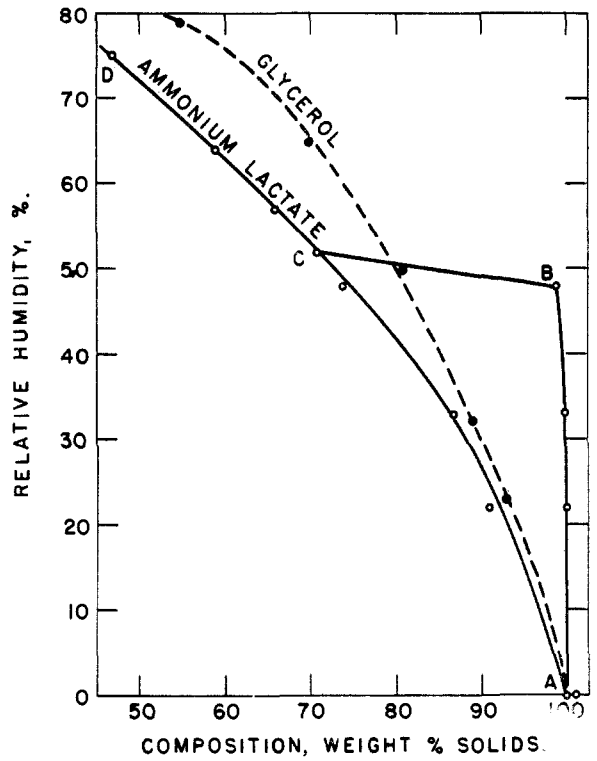

Fig. 1.—Hygroscopicity of ammonium lactate at 25°.

of zero and 33% crystallized when seeded with solid ammonium lactate. Although other equilibrium compositions were not tested in this manner, presumably all compositions between C and A of curve DCA (Fig. 1) would be supersaturated solutions of ammonium lactate.

TABLE II

HYGROSCOPICITY OF AMMONIUM LACTATE AT 25°

Relative humidity, %	Equilibrium compn., % NH_4 lactate Absorp.[a]	Desorp.[b]	Relative humidity, %	Equilibrium compn., % NH_4 lactate Absorp.[a]	Desorp.[b]
0	100	101	52	71	..
22	100	91	57	66	..
33	100	87	64	59	59
48	99	74	75	47	..

[a] Crystalline salt exposed to the various relative humidities. [b] Equilibrium compositions, obtained by absorption, transferred to atmospheres of lower relative humidity.

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An Expression for Gradient Elution

BY ARTHUR CHERKIN, FRANK E. MARTINEZ AND MAX S. DUNN

RECEIVED SEPTEMBER 29, 1952

In discussing column chromatography Tiselius[1] has said that "one of the most important practical problems of chromatography is to eliminate tailing as far as possible." One solution to the problem is gradient elution, which has been found to reduce tailing and to improve fractionation of compounds adsorbed on columns.[1-4] In such elution the concentration of elutant is increased smoothly as elution proceeds, with the effect of accelerating the tail by a higher concentration of elutant than is present at the front.

In the usual apparatus, a relatively concentrated stock solution of elutant is added dropwise to a mixing reservoir fitted with a magnetic stirrer and partly filled with a dilute solution of elutant. A side outlet near the bottom of the reservoir is joined to the top of the chromatographic column. Since the only openings in the reservoir are the inlet and outlet, inflow and outflow rates are equal.

In using gradient elution, it is helpful to be able to pre-determine the initial and final concentrations of elutant entering the column and the total volume of eluate. To this end, the relationships of the variables involved were expressed as a differential equation which upon solution gave the general expression

$$C/C_0 = (e^K - 1)/e^K$$

where C = concentration of elutant in solution leaving reservoir; C_0 = concentration of elutant in stock solution entering reservoir; K = ratio of the volume of eluate collected to the volume of diluent in the mixing reservoir.

The values of C/C_0 obtained for different values of K are plotted in Fig. 1, which emphasizes the fact that for a linear change in elutant concentration the value of K should not exceed unity. That is to

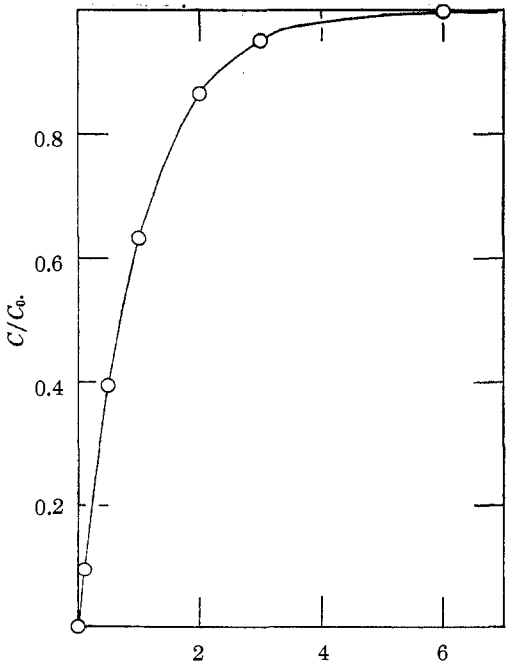

Fig. 1.—Relationship of $C/k \cdot C_0$ (ratio of concentration of elutant in solution leaving mixing reservoir to its concentration in solution entering reservoir) to K (ratio of volume of solution which has entered reservoir to volume of diluent originally placed there).

(1) A. Tiselius, *Endeavour*, **11**, 5 (1952).

(2) H. Busch, R. B. Hurlbert and V. R. Fields, *J. Biol. Chem.*, **196**, 717 (1952).

(3) K. O. Donaldson, V. J. Tulane and L. M. Marshall, *Anal. Chem.*, **24**, 185 (1952).

(4) L. Hagdahl, R. J. P. Williams and A. Tiselius, *Arkiv. Kemi*, **4**, 193 (1952).

say, the volume of diluent placed in the mixing reservoir should at least equal the volume of eluate to be collected. Furthermore, if the total volume of solution leaving the reservoir exceeds twice the original volume in the reservoir, the gradient effect of any further elution is negligible.

A more limited form of expression for gradient elution was derived empirically by Donaldson, *et al.*,[3] from experimental data.

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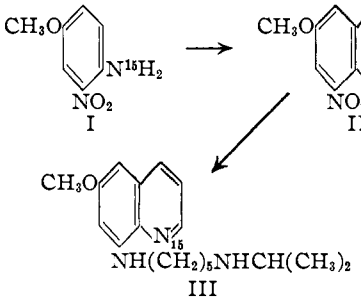
Synthesis of Pentaquine Labeled in the Quinoline Ring with N^{15} [1]

BY ROBERT C. ELDERFIELD,[2] LELAND L. SMITH AND ELEANOR WERBLE

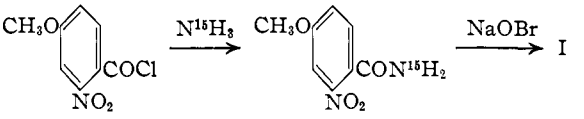
RECEIVED NOVEMBER 4, 1952

In the preceding paper the preparation of pentaquine [6-methoxy-8-(5-isopropylaminopentylamino)-quinoline] carrying N^{15} in each of the two side chain positions was described.[3] The results of a study of the excretion products of these two labeled drugs when fed to monkeys are described in an accompanying article.[4] In view of the inconclusive nature of the latter studies insofar as the physiological disposition of the drug is concerned, it was felt that a similar study of pentaquine labeled with N^{15} at the quinoline nitrogen was mandatory and might be productive of more useful information. Accordingly we wish to report at this time the synthesis of this substance. The physiological studies with the drug are under way and will be reported in a later communication.

The obvious route to the synthesis of the desired drug involves preparation of 4-methoxy-2-nitroaniline (I) carrying N^{15} in the amino group. By conventional methods 6-methoxy-8-nitroquinoline (II)[5,6] and pentaquine (III)[7] labeled at the ring nitrogen are then easily available.



A logical means for the introduction of N^{15} into I appeared to be at hand in the reaction of 4-methoxy-2-nitrochlorobenzene (IV) with potassium phthalimide enriched with N^{15}. In preliminary experiments *o*-nitrochlorobenzene reacted in good yield with potassium phthalimide in boiling dimethylformamide to yield *o*-nitroaniline after hydrolysis. However, when the same reaction was attempted with IV, the deactivating effect of the methoxyl group was sufficiently great that the analogous reaction was completely prevented. Use of higher boiling solvents or substitution of bromine or iodine for the chlorine in IV were without effect. Therefore another route to I was employed as shown by the formulas



Pentaquine monophosphate was obtained in overall yield of 25% from V by this procedure.

p-Toluidine was nitrated according to Nolting and Collin[8] to yield 4-amino-2-nitrotoluene in 65% yield. This was diazotized to 4-hydroxy-2-nitrotoluene (VI)[9] in 36% yield. Methylation of VI with dimethyl sulfate[9] gave 4-methoxy-2-nitrotoluene in 88% yield. Permanganate oxidation of the latter according to Ullmann and Dootson[10] gave 4-methoxy-2-nitrobenzoic acid. Action of N^{15}-ammonia on the acid chloride of 4-methoxy-2-nitrobenzoic acid gave the amide, m.p. 160–162° from aqueous alcohol. (*Anal.* Calcd. for $C_8H_8N_2O_4$: C, 49.0; H, 4.1; N (normal N), 14.3. Found: C, 48.19; H, 4.4; N, 14.3, 14.6). By degradation of the amide with sodium hypobromite I was obtained in 66% yield.

The pentaquine monophosphate was enriched by 19.6 atoms % excess N^{15}.[11]

(1) The work here reported was done under a grant from the National Institutes of Health to Columbia University.

(2) Department of Chemistry, University of Michigan, Ann Arbor, Michigan.

(3) A. H. Blatt and Norma Gross, THIS JOURNAL, **75**, 1245 (1953).

(4) R. C. Elderfield and L. L. Smith, *ibid.*, **75**, 1022 (1953).

(5) I. T. Strukov, *Org. Chem. Ind. (U.S.S.R.)*, **4**, 523 (1937).

(6) H. S. Mosher, W. H. Yanko and F. C. Whitmore, *Org. Syntheses*, **27**, 48 (1947).

(7) N. L. Drake, *et al.*, THIS JOURNAL, **68**, 1529 (1946).

(8) E. Nolting and A. Collin, *Ber.*, **17**, 261 (1884).

(9) D. G. Harvey and W. Robson, *J. Chem. Soc.*, 97 (1938).

(10) F. Ullmann and P. Dootson, *Ber.*, **51**, 9 (1918).

(11) The isotopic nitrogen analysis was done by Dr. D. Rittenberg of the College of Physicians and Surgeons of Columbia University to whom we wish to express our appreciation.

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Synthesis of Pentaquine Labeled in the Side Chain with N^{15} [1]

BY A. H. BLATT AND NORMA GROSS

RECEIVED NOVEMBER 4, 1952

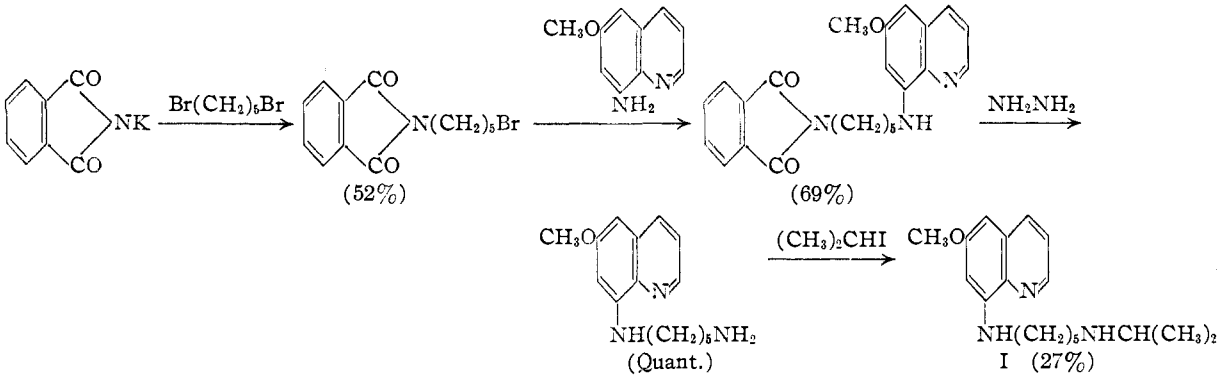
In order to permit the study of the physiological disposition of pentaquine [6-methoxy-8-(5-isopropylaminopentylamino)-quinoline (I)] described by Elderfield and Smith[2] we prepared samples of pentaquine in which (a) the terminal nitrogen atom of the side chain and (b) the nitrogen atom attached to the 8 position of the quinoline ring was labeled with N^{15}. (For convenience these substances are designated pentaquine-N^{15}(T) and pentaquine-N^{15}(8), respectively.) The synthesis of the third isomer, in which the ring nitrogen atom is

(1) The work reported in this note was done under a grant from the National Institutes of Health to Queens College.

(2) R. C. Elderfield and L. L. Smith, THIS JOURNAL, **75**, 1022 (1953).

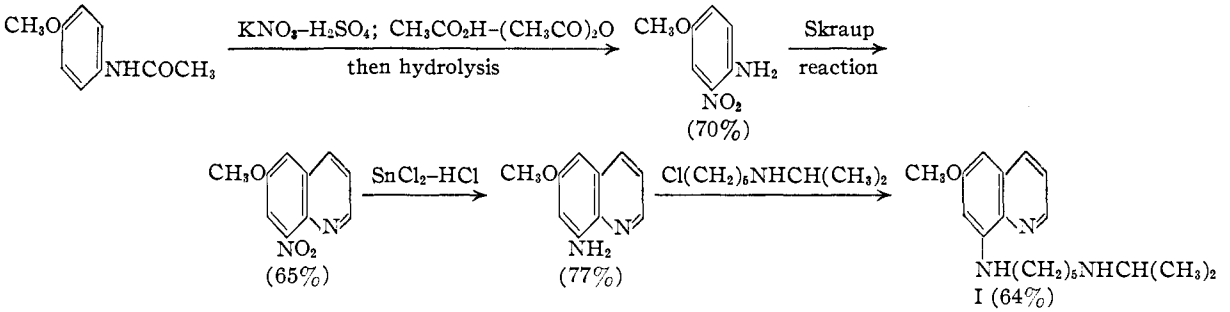
labeled with N^{15}, is described in the succeeding note by Elderfield, Smith and Werble.[3]

The synthesis of pentaquine-N^{15}(T) involved the following reactions starting with potassium phthalimide containing 62 atom per cent. excess N^{15}.



Our over-all yield in the first three reactions was 36%, compared with 39% obtained by Drake[4] whose directions were used. The final reaction, the attachment of the isopropyl group, had not been done before. Reductive alkylation with acetone gave erratic results so we alkylated with isopropyl iodide, following a procedure developed by Baldwin[5] for the corresponding alkylation with *n*-butyl iodide. The pentaquine-N^{15}(T) obtained as the monophosphate contained 20.5 atom per cent. excess N^{15} and had a 98% homogeneity by counter-current extraction.

The synthesis of pentaquine-N^{15}(8) involved the following series of reactions, in which the N^{15} was introduced in the first reaction by the use of potassium nitrate containing 62 atom per cent. excess N^{15}.



The over-all yield was 22.5%, as compared with an over-all yield of 24.7% for the same reactions as reported in the literature. The pentaquine-N^{15}(8) contained 20.0 atom per cent. N^{15}.

With one exception, available procedures[6] could be used for all the reactions in the synthesis of pentaquine-N^{15}(8). The exception is the first reaction, the nitration of acetyl-*p*-anisidine. The most satisfactory procedure for this nitration[6a] uses an excess (1.6 equivalents) of 70% nitric acid since this is less expensive than acetyl-*p*-anisidine. Concentrated nitric acid enriched in N^{15} was not available to us and we chose to use the easily handled N^{-15}-enriched potassium nitrate rather than to concentrate the dilute nitric acid. We also worked out, with unlabeled materials, conditions for the most efficient use of the nitrating agent since it is vastly much more expensive than the acetyl-*p*-anisidine. Our results, because of their possible general interest, are given in brief form.

1. Potassium nitrate and acetic acid will not nitrate acetyl-*p*-anisidine. A mineral acid is essential. Sulfuric acid is the obvious choice and it was used in all subsequent experiments.

2. Sulfuric acid cannot be used as the solvent for the nitration, for in this solvent the nitro group takes the position *ortho* to the methoxyl group. Acetic acid is obviously the solvent to choose and it was used in all subsequent experiments.

3. The nitrating agent (potassium nitrate and sulfuric acid) must be added to the solution of acetyl-*p*-anisidine in acetic acid. Addition of acetyl-*p*-anisidine in acetic acid to the nitrating agent results in the introduction of the nitro group in the *ortho* position to the methoxyl group.

4. A mixture of potassium nitrate, sulfuric acid and sufficient water to approximate 70% nitric acid is a satisfactory nitrating agent. However, some of the potassium nitrate does not dissolve and the loss would be prohibitively wasteful and expensive with potassium nitrate containing N^{15}.

5. A mixture of potassium nitrate and sulfuric acid to which sufficient water has been added to dissolve the salt is satisfactory for nitration if the acetyl-*p*-anisidine is dissolved in acetic acid plus

(3) R. C. Elderfield, L. L. Smith and E. Werble, *ibid.*, **75**, 1245 (1953).

(4) Private communication from Dr. N. L. Drake.

(5) A. W. Baldwin, *J. Chem. Soc.*, 2959 (1929).

(6) (a) Nitration; directions of H. S. Mosher, W. H. Yanko and F. C. Whitmore, made available to us by Dr. R. C. Elderfield. (b) Skraup reaction; H. S. Mosher, W. H. Yanko and F. C. Whitmore, *Org. Syntheses*, **27**, 48 (1947). (c) Reduction; directions of T. A Williamson, made available to us by Dr. R. C. Elderfield. (d) Attachment of side chain; N. L. Drake, *et al.*, THIS JOURNAL, **68**, 1529 (1946).

enough acetic anhydride to convert the added water to acetic acid.

6. It is more economical to use a slight excess of nitrating agent than to take the equivalent amount and then separate unreacted acetyl-*p*-anisidine from the nitration product.

With the information from these experiments we set up a procedure for nitrating acetyl-*p*-anisidine in acetic acid–acetic anhydride solution with a solution of potassium nitrate, sulfuric acid and water. The procedure gave satisfactory results as a comparison with the results of Mosher, Yanko and Whitmore[6a] shows.

	Equivalents of NO_3^-	Yield, % Based on acetyl-*p*-anisidine	Based on NO_3^-
Mosher, Yanko, Whitmore	1.6	85	57
This article	1.09	77	70

A more complete description of our work with full experimental details is available in microfilm.

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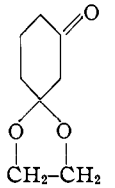
Reactions of the Monoethylene Ketal of 1,3-Cyclohexanedione

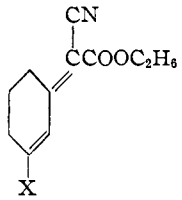
BY MARSHALL W. CRONYN AND GREGOR H. RIESSER

RECEIVED OCTOBER 31, 1952

The reactions of the monoethylene ketal of 1,3-cyclohexanedione[1] (I) have been investigated in more detail in an effort to obtain certain 3-substituted cyclohexanones which could be of value as intermediates in the preparation of 5-substituted morphans.



I



II, X = NH_2
III, X = $NHCH_2C_6H_5$
IV, X = OH
V, X = OCH_2CH_2OH

Reaction of the monoethylene ketal (I) with ethyl cyanoacetate in alcoholic ammonia did not give the expected Guareschi imide,[2] as shown both by its insolubility in dilute alkali and by its elemental analysis, $C_{11}H_{14}N_2O_2$. The analysis and the ultraviolet absorption spectrum indicated that the product, obtained in 82–90% yield, was ethyl α-cyano-3-amino-2-cyclohexene-$\Delta^{1,\alpha}$-acetate (II). Evidence for the structure of II was obtained by hydrolysis to the corresponding enol (IV), whose absorption spectrum was quite similar, and by the independent synthesis of both II and IV.

The enol (V) was synthesized by condensation of the monoethylene ketal (I) with ethyl cyanoacetate in chloroform with acetic acid and ammonium acetate.[3] The crude material obtained by distillation of the Knoevenagel reaction product was a mixture of the enol (V) and the corresponding cyclic ketal.

When the enol ether (V) was treated with alcoholic ammonia there was an immediate reaction and the eneamine (II) was obtained. Thus, under the Guareschi conditions, II must be obtained from the monoethylene ketal (I) by means of a Knoevenagel type reaction followed by opening of the cyclic ketal to the enol ether (V) and 1,6-addition of ammonia with elimination of the ethylene glycol.

As would be expected of a vinylog of an amide, II is a neutral compound, soluble only in concentrated hydrochloric or sulfuric acids; upon immediate dilution the eneamine is recovered unchanged. Refluxing II in either acidic or alkaline solution gives the enol (IV). As a vinylog of an acyl cyanoacetate[4] the enol is acidic enough to be titrated quantitatively to the phenolphthalein end-point.

Extensive hydrolysis of the eneamine (II) in acid solution gave 3-methyl-2-cyclohexene-1-one. This is analogous to the hydrolysis and decarboxylation of diethyl 3-oxo-2-cyclohexene-1-methylmalonate previously reported.[5]

The monoethylene ketal (I) was condensed with cyanoacetic acid in the presence of ammonium acetate[6] and there was obtained, in low yield, the ethylene ketal of 3-oxo-1-cyclohexeneacetonitrile.

A reductive condensation[7] with ethyl cyanoacetate proceeded readily to the ethylene ketal of ethyl 3-oxo-cyclohexaneacetate. Hydrolysis and decarboxylation of this ketal gave 3-oxo-cyclohexaneacetic acid.

Attempted reductive amination of the monoethylene ketal (I) gave no reproducible results.

Experimental[8]

Monoethylene Ketal of 1,3-Cyclohexanedione.—The preparation as described previously[1] was simplified by extraction of the ketal from the benzene solution with 2 *N* sodium metabisulfite. A 35% yield of pure ketal was obtained after saturation with potassium carbonate, extraction with chloroform and distillation.

Ethyl α-Cyano-3-amino-2-cyclohexene-$\Delta^{1,\alpha}$-acetate (II).—A mixture of 31.2 g. (0.2 mole) of the monoethylene ketal of 1,3-cyclohexanedione (I) and 25 g. (0.22 mole) of ethyl cyanoacetate were placed in a citrate bottle with 75 ml. of absolute alcohol saturated at −10° with ammonia (*ca.* 15 g. of ammonia). The solution turned yellow, became warm and after about 30 min. a precipitate separated. After an hour the reaction had subsided and the solution was cooled in ice and filtered. The product was washed with water and air-dried to give 30 to 37 g. (82–90% yield) of yellow crystalline material melting at 230–233° with dec. An analytical sample was prepared by recrystallization from 95% ethanol and from dimethylformamide–water, m.p. 232–233.5° dec.

Anal. Calcd. for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.59; mol. wt., 206. Found: C, 63.97; H, 6.74; N, 13.32; mol. wt., 196.

(1) M. W. Cronyn and J. E. Goodrich, THIS JOURNAL, **74**, 3331 (1952).

(2) I. Guareschi, *Gazz. chim. ital.*, **48**, II, 83 (1918).

(3) A. C. Cope and E. M. Hancock, *Org. Syntheses*, **25**, 46 (1945); E. J. Cragoe, C. M. Robb and J. M. Sprague, *J. Org. Chem.*, **15**, 381 (1948).

(4) G. E. K. Branch and M. Calvin, "The Theory of Organic Chemistry," Prentice-Hall, Inc., New York, N. Y., 1941, p. 268.

(5) C. Clemo, W. Cocker and S. Hornsby, *J. Chem. Soc.*, 616 (1946).

(6) D. E. Whyte and A. C. Cope, THIS JOURNAL, **65**, 1999 (1943).

(7) E. R. Alexander and A. C. Cope, *ibid.*, **66**, 886 (1944).

(8) Analyses by the Microanalytical Laboratory of the Department of Chemistry, University of California. The ultraviolet absorption spectra were taken in 95% ethanol using a Beckman model DU spectrophotometer. All melting points are corrected.

Ultraviolet absorption, λ_{max} 226 mμ, log ϵ 4.00 and λ_{max} 381 mμ, log ϵ 4.76 with a minimum at 283 mμ, log ϵ 1.78.

Butyl α-Cyano-3-amino-2-cyclohexene-Δ1,α-acetate.—The *n*-butyl ester was obtained in the same manner, m.p. 142–143° after recrystallization from benzene–ethanol.

Anal. Calcd. for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74. Found: C, 66.65; H, 7.63.

Ethyl α-Cyano-3-(N-benzylamino)-2-cyclohexene-Δ1,α-acetate (III).—When a mixture of the monoketal, ethyl cyanoacetate and benzylamine was allowed to stand at 40° for 6 days, the N-benzyl derivative crystallized upon cooling the solution, m.p. 135–137°. An analytical sample was obtained by two crystallizations from 95% ethanol, m.p. 139–139.5°.

Anal. Calcd. for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.46. Found: C, 72.81; H, 7.07; N, 9.73.

Ultraviolet absorption, λ_{max} 386 mμ, log ϵ 4.80; λ_{max} 227 mμ, log ϵ 4.04.

Ethyl α-Cyano-3-hydroxy-2-cyclohexene-Δ1,α-acetate (IV).

a. By Alkaline Hydrolysis.—The enamine ester (II) (2.08 g., 0.01 mole) was heated for 3.5 hr. in 100 ml. of refluxing 1 *N* alcoholic potassium hydroxide. The ammonia evolved was absorbed in 0.1 *N* hydrochloric acid; titration showed 0.93 mole equivalent of ammonia absorbed. A small amount of unreacted starting material was removed by filtration and the solution was concentrated *in vacuo* and acidified. There was obtained 1.4 g. (67%) of the light tan crystalline acid, m.p. 139–141°. An analytical sample was obtained by crystallization from cyclohexane–ethyl acetate, m.p. 142–143.5°; ultraviolet absorption, λ_{max} 343 mμ, log ϵ 4.44.

Anal. Calcd. for $C_{11}H_{13}NO_3$: C, 63.75; H, 6.32; N, 6.76; neut. equiv., 207. Found: C, 64.01; H, 6.37; N, 6.57; neut. equiv., 209.

b. By Acid Hydrolysis (4.5 Hr.).—A solution of 4 g. of (II) in 20 ml. of water and 20 ml. of ethanol with 7 ml. of concentrated sulfuric acid was allowed to reflux for 4.5 hr. The solution was filtered, concentrated and diluted with 30 ml. of water. After recrystallization of the product from ethanol there was obtained 1.4 g. of material melting at 139–141° and with no depression in melting point when mixed with a sample obtained by alkaline hydrolysis.

c. Acid Hydrolysis (24 Hr.).—A solution of 4 g. of the enamine ester (II) was heated for 24 hr. in 20 ml. of 50% ethanol and 5 ml. of concentrated sulfuric acid. The alcohol was removed, the solution was diluted with water and it was then extracted with chloroform. From the chloroform there was obtained 0.4 g. of 3-methyl-2-cyclohexene-1-one, b.p. 60–61° at 4 mm., $n^{25}D$ 1.4915. The 2,4-dinitrophenylhydrazone, m.p. 175–177° after crystallization from ethanol–ethyl acetate, gave no depression in m.p. when mixed with the 2,4-dinitrophenylhydrazone of an authentic sample.[1]

Knoevenagel Reaction with the Monoketal (I).—The ketal (7.7 g., 0.05 mole), ethyl cyanoacetate (11.3 g., 0.1 mole), acetic acid (4.8 g.), and 50 ml. of chloroform were heated under a soxhlet extractor containing anhydrous magnesium sulfate in the thimble. One-half gram portions of ammonium acetate were added after 5 min., 1 hr., 3 hr. and 5 hr. After 6 hr. the solution was washed with water and 8% bicarbonate. Removal of the volatile material by distillation *in vacuo* followed by distillation of the residue at 215–230° (3 mm.) gave a solid which was recrystallized from methylcyclohexane–ethyl acetate to give 3.4 g. (27%) of **ethyl α-cyano-3-(β-hydroxyethyl)-2-cyclohexene-Δ1,α-acetate**, m.p. 105–108°. Recrystallization from benzene–petroleum ether gave an analytical sample, m.p. 112–112.5°; ultraviolet absorption, λ_{max} 339 mμ, log ϵ 4.24.

Anal. Calcd. for $C_{12}H_{17}NO_4$: C, 62.03; H, 6.84; N, 5.58. Found: C, 61.74; H, 6.85; N, 5.77.

Fractionation of the product from another experiment starting with 15 g. of the ketal (I) gave 3.2 g. of a fraction, b.p. 174° (0.2 mm.), $n^{25}D$ 1.4901, and a higher boiling fraction, 1.2 g. at 200–210°. The 200–210° fraction solidified immediately upon cooling while the 174° fraction solidified slowly after several weeks.

One gram of the ketal (174° fraction) dissolved in 5 ml. of 95% ethanol and 5 ml. of 6 *N* hydrochloric acid gave upon standing 0.6 g. of light tan solid, m.p. 134–136°. Recrystallization from methylcyclohexane–ethyl acetate gave material melting at 142–143° and unchanged when mixed with the enol (IV). The same procedure applied to the solid (V), gave 0.54 g. of the enol, m.p. 141–142°; a mixed melting point with IV was undepressed.

Reaction of V with Ammonia to Give II.—Five hundred milligrams of crude V dissolved in 10 ml. of methanol and 10 ml. of aqueous ammonia gave, after 15 min., 350 mg. of yellow crystals, m.p. 231–232° with no depression when mixed with a sample of II.

Ethylene Ketal of 3-Oxo-1-cyclohexene-1-acetonitrile.—The monoketal (I) (15.6 g.), cyanoacetic acid (9.5 g.) and ammonium acetate (0.45 g.) were heated in 50 ml. of refluxing benzene under a constant water separator for 2 hr., another portion of 0.15 g. of ammonium acetate was added and the heating was continued for 6 hr. Removal of the solvent and distillation of the residue up to 180° and 1 mm. gave 9.4 g. of crude material which was fractionated to give 4.5 g. (25%) of a light yellow oil, b.p. 122–127° at 2 mm., $n^{22}D$ 1.5002. The 2,4-dinitrophenylhydrazone was recrystallized from ethanol–ethyl acetate to give small red prisms, m.p. 187–188.5°.

Anal. Calcd. for $C_{14}H_{13}N_5O_4$: C, 53.33; H, 4.16; N, 22.23. Found: C, 53.50; H, 3.90; N, 22.45.

Ethylene Ketal of Ethyl α-Cyano-3-oxo-cyclohexane-1-acetate.—A solution of 7.7 g. (0.05 mole) of I and 11.3 g. (0.1 mole) of ethyl cyanoacetate in 20 ml. of absolute ethanol was shaken for 20 hr. under 35 lb. hydrogen pressure with 0.2 g. of 5% palladium–charcoal catalyst.[9] Fractionation of the product gave 7.4 g. (58%) with a b.p. of 151–152° at 0.8 mm. and $n^{23}D$ 1.4722.

Anal. Calcd. for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.86; H, 7.64; N, 5.26.

3-Oxo-cyclohexaneacetic Acid.—The crude ketal prepared as described above was hydrolyzed by heating in 30 ml. of acetic acid and 20 ml. of concentrated hydrochloric acid for 16 hr. Crystallization of the crude product from benzene gave 1.3 g. of acid, m.p. 79.5–81° (lit. 81–82°).[10]

(9) American Platinum Works, Newark, N. J.

(10) P. D. Bartlett and G. F. Woods, THIS JOURNAL, **62**, 2933 (1940).

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Some Ethers of Pentaerythritol and Their Nitrate Esters[1]

BY ROBERT EVANS AND J. A. GALLAGHAN

RECEIVED NOVEMBER 3, 1952

The allylation of pentaerythritol to form a mixture of monoallyl and diallyl ethers as the principal products has been accomplished by a modification of the method of Nichols and Yanovsky[2] for the partial allylation of pentaerythritol.

Experimental

Preparation of Mono- and Diallyl Pentaerythritol Ethers.—A suspension consisting of 273 g. of pentaerythritol and 300 g. of *p*-dioxane was placed in a three-necked flask equipped with a mercury-sealed stirrer, a dropping funnel and a reflux condenser. A mixture of 80 g. of sodium hydroxide and 36 g. of water was slowly added to the suspension with vigorous stirring. The temperature of the reaction mixture was increased to 45°, 153 g. of allyl chloride was added, and the temperature was maintained at 45° for an additional nine hours. The cooled mixture was filtered to remove sodium chloride and unreacted pentaerythritol and concentrated. The residual mixture of allyl pentaerythritol ethers was fractionated at 1 mm. pressure.

Diallyl pentaerythritol ether, b.p. 120° (1 mm.), $n^{20}D$ 1.4729, d^{20}_{20} 1.046, was obtained in a yield of 35% based on the allyl chloride. *Anal.* Calcd. for $C_{11}H_{20}O_4$: C, 61.08; H, 9.32. Found: C, 61.25; H, 9.09.

(1) Publication approved by the Bureau of Ordnance, Navy Department.

(2) P. L. Nichols, Jr., and E. Yanovsky, THIS JOURNAL, **67**, 46 (1945).

Dinitrate Ester: $n^{20}D$ 1.4688, d^{20}_{20} 1.191. *Anal.* Calcd. for $C_{11}H_{18}N_2O_8$: C, 43.14; H, 5.92; N, 9.15. Found: C, 42.95; H, 6.08; N, 8.82.

Monoallyl Pentaerythritol Ether: b.p. 148–150° (1 mm.), $n^{20}D$ 1.4843, d^{20}_{20} 1.135, was obtained in 35% yield. *Anal.* Calcd. for $C_8H_{16}O_4$: C, 54.53; H, 9.15. Found: C, 54.50; H, 9.12.

Trinitrate Ester: $n^{20}D$ 1.4797, d^{20}_{20} 1.373. *Anal.* Calcd. for $C_8H_{13}N_3O_{10}$: C, 30.87; H, 4.21; N, 13.50. Found: C, 31.01; H, 3.93; N, 13.53.

Monopropyl Pentaerythritol Ether.—A solution of 35.2 g. of monoallyl pentaerythritol ether in 400 ml. of 95% ethanol was hydrogenated at room temperature and atmospheric pressure, using 0.2 g. of platinum oxide. The product was distilled at 125° (1 mm.), $n^{20}D$ 1.4662, d^{20}_{20} 1.096. *Anal.* Calcd. for $C_8H_{18}O_4$: C, 53.91; H, 10.18. Found: C, 53.57; H, 10.25.

Trinitrate Ester: $n^{20}D$ 1.4654, d^{20}_{20} 1.332. *Anal.* Calcd. for $C_8H_{15}N_3O_{10}$: C, 30.67; H, 4.83; N, 13.42. Found: C, 30.67; H, 4.77; N, 13.65.

Dipropyl Pentaerythritol Ether.—A solution of 25 g. of diallyl pentaerythritol in 175 ml. of 95% ethanol was hydrogenated at room temperature and atmospheric pressure, using 0.2 g. of platinum oxide. The product was distilled at 115° (1 mm.), $n^{20}D$ 1.4461, d^{20}_{20} 0.993. *Anal.* Calcd. for $C_{11}H_{24}O_4$: C, 59.97; H, 10.98. Found: C, 59.83; H, 11.06.

Dinitrate Ester: $n^{20}D$ 1.4470, d^{20}_{20} 1.144. *Anal.* Calcd. for $C_{11}H_{22}N_2O_8$: C, 42.57; H, 7.15; N, 9.03. Found: C, 42.59; H, 7.15; N, 9.15.

Monoglycerol Pentaerythritol Ether.—A mixture of 15 g. of monoallyl pentaerythritol ether, 100 ml. of 95% ethanol and 0.015 g. of osmium tetroxide dissolved in 5 ml. of water was placed in a three-necked flask equipped with a stirrer and dropping funnel. The temperature of the mixture was adjusted to 20° and 100 g. of cold 3% hydrogen peroxide was added dropwise with slow stirring. The reaction mixture was maintained at 0° overnight, then concentrated and subjected to molecular distillation. The distillate formed sugar-like crystals which softened at 55° and melted at 59–61°. *Anal.* Calcd. for $C_8H_{18}O_6$: C, 45.71; H, 8.64. Found: C, 45.91; H, 8.63.

Pentanitrate Ester: m.p. 54.5–55.0°; $n^{31}D$ 1.531, 1.520; d^{20}_{20} 1.57. *Anal.* Calcd. for $C_8H_{13}N_5O_{16}$: C, 22.03; H, 3.00; N, 16.09. Found: C, 22.15; H, 2.97; N, 15.92.

Diglycerol Pentaerythritol Ether.—Diglycerol pentaerythritol ether was prepared by hydroxylating diallyl pentaerythritol ether. The method of preparation was similar to that used for the preparation of monoglycerol pentaerythritol ether from monoallyl pentaerythritol ether. The product crystallized after molecular distillation, m.p. 72.5–74.0°, softening at 69°, when heated rapidly (Fisher–Johns melting point apparatus). *Anal.* Calcd. for $C_{11}H_{24}O_8$: C, 46.47; H, 8.51. Found: C, 46.67; H, 8.43.

Hexanitrate Ester: $n^{20}D$ 1.4878, d^{20}_{20} 1.540. *Anal.* Calcd. for $C_{11}H_{18}N_6O_{20}$: C, 23.83; H, 3.27; N, 15.16. Found: C, 23.96; H, 3.08; N, 14.87.

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Functional Aromatic Silanes

BY KURT C. FRISCH AND PHIROZE D. SHROFF

RECEIVED SEPTEMBER 4, 1952

The preparation of aromatic silane derivatives containing nuclear substituted functional groups has been the subject of a series of recent investigations.[1–6]

Roberts, McElhill and Armstrong[1] described the preparation of *m*- and *p*-trimethylsilylbenzoic acid (I) *via* the Grignard reaction as well as by means of the corresponding lithium derivative.

In the present investigation the preparation of the *p*-trimethylsilylbenzoyl chloride (II) and the corresponding amide (III) was undertaken. The synthesis of the *p*-trimethylsilylbenzoyl chloride presented somewhat of a problem because of the well-known tendency of silyl groups connected to an aromatic ring to undergo cleavage in acid medium particularly at elevated temperatures. It therefore became necessary to adopt a procedure using mild conditions and working if possible at low temperatures. This was accomplished by using thionyl chloride in the presence of pyridine as a hydrohalogen acceptor

$$\underset{\text{I}}{(CH_3)_3SiC_6H_4COOH} + SOCl_2 \xrightarrow{\text{pyridine}} \underset{\text{II}}{(CH_3)_3SiC_6H_4COCl}$$

The above reaction required less than ten minutes and the resulting acid chloride reacted with an excess of cold concd. ammonium hydroxide which yielded instantly the corresponding amide (III).

$$\underset{\text{II}}{(CH_3)_3SiC_6H_4COCl} + NH_4OH \longrightarrow \underset{\text{III}}{(CH_3)_3SiC_6H_4CONH_2}$$

Silicon-containing aromatic aldehydes have hitherto not been reported in literature. *p*-Trimethylsilylbenzaldehyde (VI) was prepared by reaction of *p*-trimethylsilylphenylmagnesium bromide (IV) with ethyl orthoformate followed by hydrolysis of the resulting acetal (V)

$$\underset{\text{IV}}{(CH_3)_3SiC_6H_4MgBr} + HC(OC_2H_5)_3 \longrightarrow \underset{\text{V}}{(CH_3)_3SiC_6H_4CH(OC_2H_5)_2} \longrightarrow \underset{\text{VI}}{(CH_3)_3SiC_6H_4CHO}$$

The acetal was not isolated in pure form but was used directly in the hydrolysis step to yield the aldehyde (VI). Remarkable is the fact that *p*-trimethylsilylbenzaldehyde can be steam distilled from an acid solution without undergoing cleavage of the C (phenyl)–Si bond.

The synthesis of silicon-containing phenols is of very recent origin. Gilman and Nobis[7] in 1950 reported several unsuccessful attempts to prepare *o*- and *m*-trimethylsilylphenol by various methods and concluded that such phenols were unstable structures.

Sunthankar and Gilman,[8] however, succeeded in preparing trimethyl- and triphenylsilylnaphthols by the reaction of chlorosilanes with the corresponding naphthyllithium compounds.

After the present work was completed Speier[2] reported the successful synthesis of *o*- and *p*-trimethylsilylphenol by the reaction of *o*- and *p*-chlorophenoxytrimethylsilane with sodium and trimethylchlorosilane. The same investigator also reported that magnesium could not be used in place of sodium when used with *p*-bromophenoxytrimethylsilane.

(1) J. D. Roberts, E. A. McElhill and R. Armstrong, THIS JOURNAL, **71**, 2925 (1949).
(2) J. L. Speier, *ibid.*, **74**, 1003 (1952).
(3) R. A. Benkeser and P. E. Brumfield, *ibid.*, **73**, 4770 (1951).
(4) D. W. Lewis and G. C. Gainer, *ibid.*, **74**, 2931 (1952).
(5) B. N. Dolgov and O. K. Panina, *Zhur. Obshchei Khim.* (*J. Gen. Chem.*), **18**, 1129 (1948); *C. A.*, **43**, 1737 (1949).
(6) A. J. Barry and J. W. Gilkey, U. S. Patent 2,601,237 (1952).
(7) H. Gilman and J. F. Nobis, THIS JOURNAL, **72**, 2629 (1950).
(8) S. V. Sunthankar and H. Gilman, *ibid.*, **72**, 4884 (1950).

In the present work the Grignard reagent of *p*-bromophenoxytrimethylsilane (VII) reacted with trimethylchlorosilane

$$(CH_3)_3SiOC_6H_4MgBr + (CH_3)_3SiCl \longrightarrow (CH_3)_3SiOC_6H_4Si(CH_3)_3$$
VII VIII

The hydrolysis of (VIII) to the free phenol (IX) was accomplished by treatment with acidified dilute ethanol

$$(CH_3)_3SiOC_6H_4Si(CH_3)_3 \longrightarrow HOC_6H_4Si(CH_3)_3$$
VIII IX

Experimental

***p*-Trimethylsilylbenzoic acid** (I) was prepared *via* the Grignard reaction using essentially the procedure of Roberts, McElhill and Armstrong.[1] The pure compound crystallized in colorless needles, m.p. 117–118° (uncor.).

***p*-Trimethylsilylbenzoyl Chloride** (II).—In an erlenmeyer flask was placed 11.5 g. of *p*-trimethylsilylbenzoic acid, 4.7 g. of pyridine and 75 cc. of ether. A solution of 7.1 g. of thionyl chloride in 100 cc. of ether was gradually added with shaking. A white precipitate formed. After shaking for about ten minutes, pyridine hydrochloride was filtered off and the ethereal solution of the acid chloride was used directly for the preparation of the amide.

***p*-Trimethylsilylbenzamide** (III).—The ethereal solution of the acid chloride (II) was added dropwise to an excess of concd. ammonium hydroxide solution, cooled by means of an ice-bath. Immediately a white precipitate formed. The solvent was removed and the precipitate filtered and washed repeatedly with cold water. The acid amide formed colorless plates, m.p. 153° (uncor.). The yields were between 70–80% based on the amount of acid used.

Anal. Calcd. for $C_{10}H_{15}ONSi$: Si, 14.5; N, 7.2. Found: Si, 14.8; N, 6.9.

***p*-Trimethylsilylbenzaldehyde** (IV).—To the Grignard solution, made from 62.1 g. of *p*-bromophenyltrimethylsilane, was added a solution of 40.2 g. of ethyl orthoformate in 100 cc. of ether. The mixture was refluxed for 14 hours. It was then ether extracted and the solvent afterwards removed. The residual, brown solid mass was ground up into a fine powder and was slowly added to 750 cc. of a 6% hydrochloric acid solution which was maintained at about 5° by means of an ice-bath. After all the powder had been dissolved it was stirred for four hours and the temperature rose to room temperature. The mixture was ether extracted and the solvent removed. The residual material, representing the acetal (V), was added to 700 cc. of an aqueous solution, containing 100 g. of concd. sulfuric acid. The mixture was refluxed for 15 minutes. Low-boiling material was first removed by distillation. The residual liquid was steam-distilled. The distillate was ether extracted and the solvent afterwards removed. The residual oil crystallized on seeding with a crystal of the aldehyde. The crude yield was 96%. The aldehyde can be purified by recrystallization from ligroin, forming colorless needles, m.p. 109–110° (uncor.). It can also be purified by vacuum distillation, b.p. 119° at 15 mm.

Anal. Calcd. for $C_{10}H_{14}OSi$: Si, 15.73. Found: Si, 15.9.

Infrared analysis showed the presence of carbonyl, phenyl, Si–CH_3 and Si–C.

The 2,4-dinitrophenylhydrazone of *p*-trimethylsilylbenzaldehyde formed reddish-orange crystals and recrystallized from alcohol and ethyl acetate melted at 209° (uncor.). The infrared analysis indicated the presence of N–H, Si–CH_3, Si–C, $-NO_2$ and phenyl, accounting well for the structure of the 2,4-dinitrophenylhydrazone.

***p*-Bromophenoxytrimethylsilane**.—This compound, previously described by Speier,[2] was prepared from *p*-bromophenol and trimethylchlorosilane using pyridine as hydrohalogen acceptor. The yield was 76–85%.

Anal. Calcd. for $C_9H_{13}OBrSi$: Si, 11.4. Found: Si, 11.3.

***p*-Trimethylsiloxyphenylmagnesium Bromide** (VII).—In a three-necked flask were placed 19 g. of magnesium turnings and 200 cc. of anhyd. ether. A solution of 185 g. of *p*-bromophenoxytrimethylsilane in 200 cc. of ether was gradually added through the dropping funnel. The mixture was then refluxed for 18 hours; 3.8 g. of magnesium was recovered, indicating a 83% yield of the Grignard reagent.

***p*-Trimethylsilylphenoxytrimethylsilane** (VIII).—Half of the above Grignard solution (VII) was slowly added to a solution of 42.7 g. of trimethylchlorosilane in 150 cc. of ether. The mixture was then refluxed for three hours. The inorganic precipitate was filtered off and washed with ether. The ether was removed from the filtrate and the residual liquid fractionated. The product distilled at 114–115° at 20 mm. as a colorless liquid.

Anal. Calcd. for $C_{12}H_{22}OSi_2$: Si, 23.5. Found: Si, 22.0.

The product was slightly impure probably due to contamination by some *p*-bromophenoxytrimethylsilane.

***p*-Trimethylsilylphenol** (IX).—The hydrolysis of the trimethylsiloxy group could not be brought about by mere treatment in dilute acid at room temperature probably due to the insolubility of the compound. Ether extraction of the product, followed by fractionation, resulted in an almost complete recovery of the starting product. The hydrolysis was effected as follows:

10.2 g. of *p*-trimethylsilylphenoxytrimethylsilane (VIII) was added to a solution of 100 cc. of ethanol and 60 cc. of water. The solution was slightly acidified with hydrochloric acid. The mixture was refluxed for one hour, leaving a solid which was recrystallized several times from water, yielding colorless needles, m.p. 74–75° (uncor.). This is in good agreement with the melting point reported by Speier,[2] m.p. 74–74.2°.

Anal. Calcd. for $C_9H_{14}OSi$: Si, 16.9. Found: Si, 16.6.

NEW PRODUCTS DEVELOPMENT LABORATORY
GENERAL ELECTRIC COMPANY, CHEMICAL DIVISION
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Some Reactions of Pentaphenylchlorodisilane

BY HENRY GILMAN AND JACK J. GOODMAN

RECEIVED OCTOBER 6, 1952

The reactions of pentaphenylchlorodisilane have been studied to determine their relationship to those of analogous monosilane compounds, and to test the stability of the Si–Si bond in this hexasubstituted unsymmetrical disilane series.

The reaction of pentaphenylchlorodisilane with primary alcohols proceeds smoothly to give the corresponding pentaphenylalkoxydisilanes. Analogous reactions in the monosilane series have given

$$(C_6H_5)_3SiSi(C_6H_5)_2Cl + RCH_2OH \longrightarrow (C_6H_5)_3SiSi(C_6H_5)_2OCH_2R + HCl$$

similar results.[1] Attempts to make the corresponding derivatives of secondary or tertiary alcohols, under conditions used for the preparation of primary alkoxides from pentaphenylchlorodisilane, failed. The preparation of secondary and tertiary alkoxymonosilanes, however, has been reported.[2,3] These results may indicate a characteristic difference between the di- and monosilanes of this type. It is believed that the factor of steric hindrance might be in large part responsible for the anomalous results obtained.

The preparation of pentaphenylhydroxydisilane by the hydrolysis of pentaphenylchlorodisilane

(1) R. O. Sauer, THIS JOURNAL, **66**, 1707 (1944).

(2) R. H. Krieble and C. A. Burkhard, *ibid.*, **69**, 2689 (1947); M. N. Kalinin, *Compt. rend. acad. Sci. (U.S.S.R.)*, **26**, 365 (1940) [*C. A.*, **35**, 2470 (1941)]; C. S. Miner, Jr., L. A. Bryan and R. P. Holysz, Jr., *Ind. Eng. Chem.*, **39**, 1368 (1947).

(3) Privately communicated studies by Dr. G. N. R. Smart, who has observed some interesting results in reactions between the sterically hindered *o*-Tol_4SiCl and ROH and RONa compounds.

in aqueous basic media, as previously reported,[4] was unsuccessful. With both 5% and 1% ethanolic potassium hydroxide, cleavage of the Si–Si bond results. The only products so far isolated were triphenylsilanol and hexaphenyldisiloxane. The hydroxydisilane was prepared in good yield by

$$(C_6H_5)_3SiSi(C_6H_5)_2Cl + KOH \xrightarrow[H_2O]{C_2H_5OH} (C_6H_5)_3SiOH + (C_6H_5)_3SiOSi(C_6H_5)_3$$

the hydrolysis of pentaphenylchlorodisilane with water in dioxane. In this connection it is interesting to note that whereas the reaction of triphenylsilanol with formic acid gave hexaphenyldisiloxane,[5] the corresponding *sym*-bis-(triphenylsilyl)-tetraphenyldisiloxane, $(C_6H_5)_3SiSi(C_6H_5)_2$-O-$(C_6H_5)_2SiSi(C_6H_5)_3$, could not be made by the analogous reaction with pentaphenylhydroxydisilane.

When treated with phenyllithium, pentaphenylchlorodisilane was converted in good yield into hexaphenyldisilane.[6] A similar reaction of pentaphenylethoxydisilane with phenyllithium also gave an excellent yield of this compound. In this respect the unsymmetrical disilanes gave results identical with those obtained for the monosilane series.[7]

Experimental conditions[8] in essential accordance with those for the preparation of triphenylsilane were employed to make pentaphenyldisilane. Reaction of this compound with phenyllithium gave a quantitative yield of hexaphenyldisilane.[9]

Experimental

Pentaphenylethoxydisilane.—To 20.0 g. (0.435 mole) of absolute ethanol[10] was added slowly and with stirring 2.0 g. (0.0042 mole) of pentaphenylchlorodisilane.[11] The mixture was refluxed with stirring on a water-bath for one hour. At no time did complete solution take place. After cooling the reaction mixture, which was acid to litmus, a solid material was filtered off. There was obtained 1.84 g. of a white powder melting at 207–211°. On standing there was separated from the mother liquors 0.15 g. of material melting at 207–210°. Two recrystallizations of total solids from petroleum ether (b.p. 60–70°) gave 1.70 g. (83.3%) of product melting at 210.5–212°.

Anal.[12] Calcd. for $C_{32}H_{30}OSi_2$: Si, 11.50. Found: Si, 11.35, 11.58.

Pentaphenylbenzyloxydisilane.—To 20.0 g. (0.185 mole) of benzyl alcohol[10] was added slowly and with stirring 2.0 g. (0.0042 mole) of pentaphenylchlorodisilane. The mixture was heated and complete solution resulted at 85–90°. The solution was then heated to 135° and allowed to cool slowly. There was filtered off 1.40 g. of crystals melting at 164–167°. An additional 0.25 g. of crystals melting at 168–171° was separated from the mother liquors. Two recrystallizations of all solids from petroleum ether (b.p. 60–70°) yielded 1.35 g. (58.7%) of crystals melting at 170–171.5°.

Anal. Calcd. for $C_{37}H_{32}OSi_2$: Si, 10.20. Found: Si, 10.20, 10.31.

Reaction of secondary or *t*-butyl alcohol[9] with pentaphenylchlorodisilane gave no alkoxydisilane derivative. Since the molar quantity of organosilicon compound is so small, a minute amount of moisture in the reagents could be responsible for the product isolated, pentaphenylhydroxydisilane. Special drying techniques[13] applied to the reagents produced no desired derivative.

Attempted Preparation of Pentaphenylhydroxydisilane.—To 2.0 g. (0.0042 mole) of pentaphenylchlorodisilane was added 95 ml. of 5% ethanolic (95%) potassium hydroxide. The mixture was refluxed over a water-bath for 4 hours. More of the alcoholic hydroxide was added until the total volume was 120 ml., and complete solution resulted. After cooling, the solution was evaporated to dryness. A white solid residue was extracted several times with hot petroleum ether (b.p. 60–70°). The remaining material was water and ether extracted. The ether layer was dried, evaporated to dryness, and the residue recrystallized from petroleum ether (b.p. 60–70°). From the first petroleum ether extract there was finally isolated 0.80 g. (69%) of material melting at 142.5–144°. This solid was identified as triphenylsilanol by a mixed melting point. From the ether extract there was finally obtained 0.20 g. (8.9%) of shiny crystals melting at 220–222°. This product was identified as hexaphenyldisiloxane by a mixed melting point.

The reaction using 1% ethanolic (95%) potassium hydroxide was carried out in the same manner. The same products were isolated and in similar yields.

Pentaphenylhydroxydisilane.—To 20.0 ml. of dioxane was added 2.0 g. (0.0042 mole) of pentaphenylchlorodisilane. On gentle warming the solid dissolved. Then 10.0 g. (0.56 mole) of distilled water was added. The solution was refluxed for 5 hours and allowed to cool. There was filtered off 1.81 g. of solids melting at 111.5–115°. The material was recrystallized three times from petroleum ether (b.p. 60–70°). The first yield of product was 1.62 g. (84.4%) melting at 134–134.5°. An infrared spectrogram showed a strong absorption band for the hydroxyl group.

Anal. Calcd. for $C_{30}H_{26}OSi_2$: Si, 12.17; active H, 1.00. Found: Si, 12.15, 12.30; active H, 1.06, 1.08 (Zerewitinoff).

Attempts to prepare the *sym*-bis-(triphenylsilyl)-tetraphenyldisiloxane proved unsuccessful. Using pentaphenylhydroxydisilane and formic acid[5] (98–100%), there was obtained a 50% recovery of the starting material. From the reaction of the sodium salt of pentaphenylhydroxydisilane and pentaphenylchlorodisilane, a glass-like substance which has so far resisted crystallization was the only product isolated.

Pentaphenyldisilane.—In a dry, three-necked flask fitted with Trubore glass stirrer, gas inlet tube, and a glass stopper were placed 5.0 g. (0.011 mole) of pentaphenylchlorodisilane and 100 ml. of anhydrous ether. After the silicon compound had dissolved, there was added 4.0 g. (0.11 mole) of lithium aluminum hydride. The mixture was brought to reflux and kept there with constant stirring and under dry nitrogen for 18 hours. The excess lithium aluminum hydride was slowly destroyed with water and the reaction mixture acidified with hydrochloric acid. The ether and water layers were separated. After the water layer had been extracted with ether several times, the combined ether fractions were dried and the solvent distilled. The white residue weighed 2.01 g. Several recrystallizations from an ethanol–benzene solution gave 1.22 g. of shiny, flaky crystals with a melting point of 128–129°. The mother liquors gave an additional 0.25 g. of this material. The total yield of pentaphenyldisilane was 1.50 g. (32.3%). A Si–H bond was present in the infrared spectrogram for this compound.

Anal. Calcd. for $C_{30}H_{26}Si_2$: Si, 12.67. Found: Si, 12.50, 12.60.

Pentaphenyldisilane and Phenyllithium.—To 0.27 g. (0.00061 mole) of pentaphenyldisilane in 20 ml. of anhy-

(4) H. Gilman, T. C. Wu, H. A. Hartzfeld, G. A. Guter, A. G. Smith, J. J. Goodman and S. H. Eidt, THIS JOURNAL, **74**, 561 (1952).

(5) Unpublished studies of H. W. Melvin, Jr.

(6) Unpublished studies of S. H. Eidt.

(7) R. F. Fleming, Jr. (to Corning Glass Works), U. S. Patent 2,386,452 (October 9, 1945) [*C. A.*, **40**, 603 (1946)]; H. Gilman and R. N. Clark, THIS JOURNAL, **68**, 1675 (1946).

(8) H. Gilman and C. G. Brannen, *ibid.*, **73**, 4640 (1951).

(9) H. Gilman and S. P. Massie, *ibid.*, **68**, 1128 (1946); R. N. Meals, *ibid.*, **68**, 1880 (1946); H. Gilman and R. N. Clark, *ibid.*, **69**, 1499 (1947); H. Gilman and H. W. Melvin, Jr., *ibid.*, **71**, 4050 (1949); W. H. Nebergall, *ibid.*, **72**, 4702 (1950).

(10) Excess of alcohol was used as solvent in all cases. A product of high purity was obtained by this procedure.

(11) The preparation of pentaphenylchlorodisilane was carried out in essential accordance with the directions given in reference 4. Our yield was 66.8%.

(12) The analysis was carried out in essential accordance with the directions of H. Gilman, B. Hofferth, H. W. Melvin, Jr., and G. E. Dunn, THIS JOURNAL, **72**, 5767 (1950).

(13) L. F. Fieser, "Experiments in Organic Chemistry," 2nd ed., D. C. Heath Co., Boston, Mass., 1941, pp. 358–359.

drous ether was added 2.5 ml. (0.0021 mole) of phenyllithium.[14] The mixture was stirred under dry nitrogen with a magnetic stirrer. Within 5 minutes, a milky solution resulted. After the solution was stirred and refluxed under dry nitrogen for 4 hours, a white precipitate settled out. As the reaction mixture was hydrolyzed with distilled water, a gas was evolved. The solid was now suspended between the ether and water layers. The material was filtered off and dried. There was obtained 0.306 g. (97.8%) of white powder melting at 361–363°. This was identified by a mixed melting point as hexaphenyldisilane.

Pentaphenylethoxydisilane and Phenyllithium.—To 0.50 g. (0.0010 mole) of pentaphenylethoxydisilane in a benzene-ether solution was quickly added 2 ml. (0.0017 mole) of phenyllithium. The solution was magnetically stirred. The reaction mixture took on a milky-white appearance in 15 minutes. After 1 hour, the suspended solids were filtered off, washed with petroleum ether (b.p. 60–70°), and dried. There was obtained 0.44 g. (83%) of material melting at 361–363°. This product was identified as hexaphenyldisilane by a mixed melting point.

Acknowledgment.—The authors are grateful to Dr. V. A. Fassel and Mr. M. Margoshes for the infrared data.

(14) R. G. Jones and H. Gilman, in "Organic Reactions," Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1951, pp. 353–354.

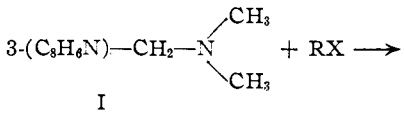
DEPARTMENT OF CHEMISTRY
IOWA STATE COLLEGE
AMES, IOWA

The Alkylation of Gramine and of Indole-N-methylgramine

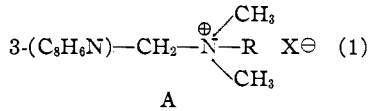
BY ALLAN P. GRAY

RECEIVED OCTOBER 15, 1952

As a result of recent investigations[1] the reaction of gramine (I) with alkyl halides has been clarified. It has been shown that the product of reaction of gramine with methyl iodide (in ethanol) is not gramine methiodide (II), as reported in the literature,[2] but is actually a mixture containing tetramethylammonium iodide, bis-(3-indolemethyl)-dimethylammonium iodide (III) together with small amounts of II. The reaction may be generalized as

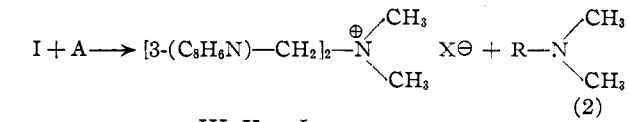


I



A

II, R = CH_3, X = I

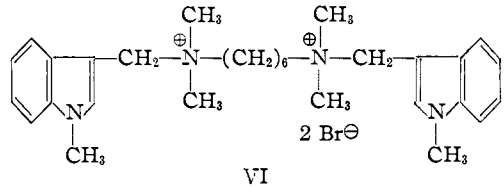


III, X = I
IV, X = Br

The relative proportions of quaternary products are naturally dependent on the proportions of reactants used, on the relative rates of reactions 1 and 2 and on solubility of the products.

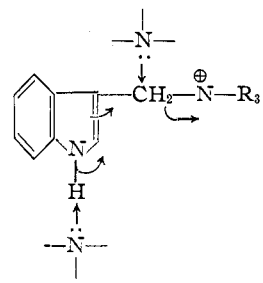
Similar results have been independently obtained in this Laboratory. In attempting to prepare a variety of quaternary derivatives, I was allowed to react with molar proportions of 1,6-dibromohexane, 1,10-dibromodecane and 1-bromohexane at room temperature in either methanol or acetonitrile. The product, which precipitated in large colorless prisms, was in each case bis-(3-indolemethyl)-dimethylammonium bromide (IV). When methanol was the solvent, IV crystallized directly from the reaction in analytically pure form.

It was of some interest to determine if indole-N-methylgramine (V) behaved in similar fashion. The possibility that it might not was supported by the fact that although prior to the recent reports[1] no complete analytical data had ever been reported for gramine methiodide,[2] a satisfactory analysis had been obtained for a sample of N-methylgramine methiodide prepared in alcohol in the ordinary way.[3] It was found that when V was allowed to react at room temperature with 1,6-dibromohexane in methanol, the main product, although somewhat difficult to separate from small amounts of impurities, was the normal 1,6-bis-quaternary derivative (VI).



VI

This does not mean that products similar to III and IV might not be obtained from N-methylgramine, but only that the displacement reaction, 2, does not take place as readily with the N-methyl base. Explanation may lie in possible lowering of the activation energy for the displacement by base-catalyzed formation of an intermediate, *viz.*



Available evidence does not permit a decision as to whether the postulated base-catalyzed elimination precedes or coincides with formation of the new C to N bond. This picture of the reaction is supported by the fact that Schöpf and Thesing[1] were able to obtain pure gramine methosulfate in good yield by neutralizing the gramine with acetic acid prior to the addition of methyl sulfate.

Acknowledgment.—Many helpful and stimulating discussions with Dr. C. J. Cavallito were deeply appreciated.

Experimental[4]

Bis-(3-indolemethyl)-dimethylammonium Bromide (IV).—The following are representative experiments in which IV was the only isolated product.

(1) T. A. Geissman and A. Armen, THIS JOURNAL, **74**, 3916 (1952); C. Schöpf and J. Thesing, *Angew. Chem.*, **63**, 377 (1951).

(2) See for example: A. Orechoff and S. Norkima, *Ber.*, **68**, 436 (1935); H. R. Snyder, C. W. Smith and J. M. Stewart, THIS JOURNAL, **66**, 200 (1944).

(3) H. R. Snyder and E. L. Eliel, *ibid.*, **70**, 1703 (1948).

(4) Microanalyses were performed by the Clark Microanalytical Laboratories, Urbana, Illinois.

A. A solution of 10 g. (0.057 mole) of gramine and 4.7 g. (0.019 mole) of 1,6-dibromohexane in 75 ml. of methanol deposited colorless prisms on standing overnight at room temperature. These were collected, washed with ethanol and then ether. After drying *in vacuo* over phosphorus pentoxide, the product melted 177–178.5° (cor.) and weighed 5.8 g. (52% yield on the basis of gramine). Additional material, which could be purified by methanol recrystallization, was recovered from the filtrates by precipitation with ether.

Anal. Calcd. for $C_{20}H_{22}N_3Br$: C, 62.50; H, 5.77; N, 10.93. Found: C, 62.78; H, 5.77.

B. Reaction of 1,10-dibromodecane with gramine in similar fashion afforded a crystalline solid which was recrystallized from methanol; m.p. alone and mixed with the product described in A was 177–178.5° (cor.).

Anal. Found: C, 62.11; H, 5.72; N, 10.80.

C. A similar reaction of 5.2 g. (0.03 mole) of gramine with 7.4 g. (0.045 mole) of 1-bromohexane in acetonitrile solution yielded 5.2 g. (92%) of crystalline precipitate after 4 days at room temperature; m.p. 178–180°, undepressed when mixed with the product from A or B. Negligible amounts of additional precipitate were obtained on addition of ether to the filtrate.

Indole-N-methylgramine (V).—N-Methylindole, b.p. 125–130° (20 mm.), $n^{23}D$ 1.6071, was prepared from indole[5] with the exception that sodium hydride was used in place of sodium. V, b.p. 113–116° (0.5 mm.), $n^{23}D$ 1.5734, was obtained from N-methylindole as described by Snyder and Eliel[3] who reported b.p. 94–96° (0.2 mm.), $n^{20}D$ 1.5743.

Reaction of V with Dibromohexane (VI).—A solution of 4.8 g. (0.026 mole) of V in 50 ml. of methanol treated with 2.1 g. (0.0086 mole) of dibromohexane yielded no precipitate after 5 days at room temperature. Addition of anhydrous ether precipitated an oil which was washed with fresh ether, dissolved in ethanol and reprecipitated. The thick viscous oil was dried over phosphorus pentoxide *in vacuo* to yield 2.4 g. of white crystalline deliquescent solid (A). The material evolved gas at 144–145°, solidified at 151° and remelted 192–202°.

A was fractionally crystallized from propanol and ether. During crystallization undue heating was avoided as decomposition appeared to take place if the solution was heated much above 50°. The head fraction, after two further recrystallizations from propanol, afforded 100 mg. of white crystals (B), m.p. 220° (decomp.). B was not further investigated.

After several recrystallizations of the mother liquor material from propanol and ether 900 mg. of white hygroscopic solid (C), which softened and evolved gas at 100°, turned red at 125° and fused at 140°, was obtained.

Anal. Calcd. for bis-(indole-N-methylgramine)quaternary salt, VI, $C_{30}H_{44}Br_2N_4$: C, 58.06; H, 7.15. Found: A: C, 57.18; H, 7.20. C: C, 57.72; H, 7.58. *Anal.* of B: C, 38.08; H, 7.83.

(5) R. Weissgerber, *Ber.*, **43**, 3520 (1910).

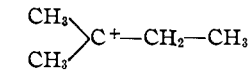
RESEARCH LABORATORIES
IRWIN, NEISLER & COMPANY
DECATUR, ILLINOIS

The Mechanism of the Acid-catalyzed Hydration of Olefins[1]

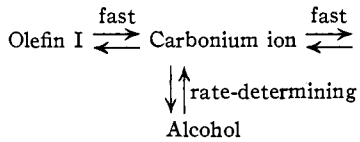
BY JOSEPH B. LEVY, ROBERT W. TAFT, JR., AND LOUIS P. HAMMETT

RECEIVED OCTOBER 18, 1952

In a study of the rates of the acid-catalyzed hydration of the two isomeric olefins trimethylethylene (I) and *asym*-methylethylethylene (II) by methods whose application to other olefins has been described[2] we have had occasion to observe that at 50% reaction neither olefin has been measurably converted to the isomer. The result is of importance in connection with the mechanism of the hydration because an identical carbonium ion (III) is obtained by the addition of a proton to



either of these olefins. Consequently, the reaction scheme consisting in the rapid and reversible addi-



tion of a proton to the olefin followed by a rate-determining reaction of the ion with a water molecule is definitely excluded as the mechanism of the hydration reaction.

The two olefins would be expected to hydrate to a single product *t*-amyl alcohol and this has been reported[3] to be the case. A further careful test on our part shows that the most probable alternative, methylisopropylcarbinol, does not constitute as much as 2% of the product of the hydration of I.

Experimental

Test for Interconversion of the Olefins.—Gaseous olefin I was shaken at 35° with 0.973 *M* nitric acid under the conditions of a rate measurement[2] until the pressure had dropped to about half of the initial value and olefin II was treated similarly at 20°. The residual olefin was then removed in each case and its infrared absorption observed in the gaseous state with a path length of 10 cm. and at a pressure equal to the vapor pressure of the olefin at 20° (*ca.* 380 mm. for I and 450 mm. for II). Under these conditions I has an absorption band with a peak at 1120 cm.$^{-1}$ for which log I_0/I was 1.2 both for the pure substance and for the partially reacted sample. At this frequency log I_0/I for II was about 0.1, both for the pure substance and for the partially reacted sample. II has a band at 1660 cm.$^{-1}$, for which log I_0/I was found to be 0.9 both for the pure substance and for the partially hydrated sample. At this frequency log I_0/I was about 0.2 both for pure I and for the partially hydrated sample.

Reaction Product.—A sample of several ml. of trimethylethylene was allowed to react at 35° for several days with 0.973 *M* nitric acid under conditions essentially identical with those prevailing during a rate measurement. The resulting solution was filtered, saturated with ammonium sulfate, and extracted with ether. The ether solution was dried and the ether evaporated through a small column. All of the residue (1.4 g.) was then distilled through the column at 99 to 102° (uncor.), $n^{25}D$ 1.4017. Under the same conditions a purified known sample of *t*-amyl alcohol boiled at 100.8 to 101.3° and had $n^{25}D$ 1.4028, and a purified known sample of methylisopropylcarbinol boiled at 110.0 to 111.0° and had $n^{25}D$ 1.4069. These values are consistent with data in the literature.

A 15% solution of the hydration product in carbon tetrachloride absorbed strongly in the infrared at 1190 cm.$^{-1}$ but not detectably at 1110 cm.$^{-1}$. *t*-Amyl alcohol has a strong broad absorption band at 1190 ± 10 cm.$^{-1}$ and methylisopropylcarbinol has a similar one at 1100 ± 10 cm.$^{-1}$. On the basis of the absorption shown at 1110 cm.$^{-1}$ by a solution containing the tertiary and secondary alcohols in the ratio of 9:1 we estimate that the hydration product cannot contain as much as 2% of the methylisopropylcar-

(1) The work reported herewith was carried out as project NR 056-062 under contract N6onr-271 between the Office of Naval Research and Columbia University. Reproduction in whole or in part permitted for any purpose of the United States Government.

(2) (a) J. B. Levy, R. W. Taft, Jr., D. Aaron and L. P. Hammett, THIS JOURNAL, **73**, 3792 (1951); (b) R. W. Taft, Jr., B. Levy, D. Aaron and L. P. Hammett, *ibid.*, **74**, 4735 (1952).

(3) (a) H. J. Lucas and Yun-Pu Liu, *ibid.*, **56**, 2138 (1934); (b) Yun-Pu Liu and Tien-Chi Wei, *J. Chinese Chem. Soc.*, **4**, 297 (1936).

binol. A sample of methylisopropylcarbinol treated with nitric acid under the same conditions as in the hydration of the trimethylethylene was not converted to the *t*-amyl alcohol to an extent measurable by the infrared spectrum.

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Preparation and Some Reactions of *n*-Heptafluoropropylmagnesium Iodide

BY O. R. PIERCE AND M. LEVINE

RECEIVED SEPTEMBER 5, 1952

An investigation of the reaction of heptafluoro-1-iodopropane with magnesium metal has been reported by Henne[1,2] and Haszeldine.[3] A study of the perfluoropropyl Grignard reagent was initiated in this Laboratory to develop techniques applicable to the preparation of a fluorine-containing silane. The investigation reported here outlines the experimental conditions which were studied in an attempt to obtain maximum yields of the Grignard reagent as indicated by addition products, using acetone, ethyl trifluoroacetate, heptafluorobutyraldehyde and 1,1,1-trifluoro-2-propanone. It should be pointed out that the Grignard reagent acts as a catalyst in aldol-type condensation reactions thereby reducing the yield of addition products in those instances in which the carbonyl compound contained α-hydrogen atoms.

Experimental

Preparation of Heptafluoro-1-iodopropane.—This material was prepared as described previously.[4]

Preparation of 3,3,4,4,5,5,5-Heptafluoro-2-methyl-2-pentanol.—Magnesium turnings, 6 g. (0.25 mole), were placed in a three-necked, round-bottom flask fitted with an efficient stirrer, separatory funnel, and reflux condenser to which was attached a Dry Ice cooled trap. The entire apparatus was dried and 100 ml. of dry tetrahydrofuran was added. A small amount of heptafluoro-1-iodopropane was introduced into the reaction flask at room temperature and the mixture was stirred vigorously until reaction had started as indicated by evolution of heat and the formation of a brown precipitate. The reaction flask was cooled immediately to −30 to −40°, and maintained at this temperature during the addition of 74 g. (0.25 mole) of heptafluoro-1-iodopropane. The extent of reaction was followed by the formation of a precipitate as the magnesium metal disappeared. The reaction became exothermic in those experiments when cooling of the reaction flask was not accomplished immediately following initiation of Grignard formation. When all the halide had been added, stirring of the mixture was continued for two hours.

Acetone, 25 g. (0.5 mole) was added dropwise at −30° and the reaction temperature was allowed to rise gradually to 25°. The reaction mixture was then hydrolyzed with water resulting in the formation of magnesium salts. The contents of the flask were then poured onto a 10% sulfuric acid–ice mixture. Upon rectification, there was obtained 20 g. of unreacted heptafluoro-1-iodopropane and 12 g. of 3,3,4,4,5,5,5-heptafluoro-2-methyl-2-pentanol, b.p. 107–108°, $n^{20}D$ 1.3250, which represents a conversion of 21% and a 48% yield. Assignment of the structure was based on agreement with the reported properties of the tertiary alcohol.[5]

Preparation of 1,1,1-Trifluoro-3,3,4,4,5,5,5-heptafluoro-2-pentanone.—The Grignard reagent was prepared as previously described. Ethyl trifluoroacetate, 18 g. (0.12 mole), was added dropwise at −30° to the reaction flask and the temperature of the mixture was allowed to warm to 25°. Heat was evolved and a gummy precipitate formed. The mixture was stirred at 50° for several hours. The reaction products were then heated to reflux and, upon cooling, were hydrolyzed with a 10% sulfuric acid–ice mixture. Upon rectification, there was obtained 18 g. (24%) of unreacted heptafluoro-1-iodopropane and 22.1 g. of material, b.p. 104–105°, $n^{20}D$ 1.3449, d^{20}_4 1.388. Since the infrared spectrum indicated the presence of a solvated ketone, this material was heated with phosphorus pentoxide, and there was obtained 15 g. (0.06 mole) of the ketone, CF_3–CO–C_3F_7, b.p. 30–31°, which represents a yield of 50% of the theoretical.

Anal. Calcd. for $C_5F_{10}O$: C, 22.57; H, 0.0; F, 71.4. Found: C, 22.28; H, 0.016; F, 70.0.

Preparation of 1,1,1,2,2,3,3,5,5,6,6,7,7,7-Tetradecafluoro-4-heptanol.—Heptafluorobutyraldehyde, 60 g. (0.3 mole), was added dropwise to the Grignard reagent (100 g. of heptafluoro-1-iodopropane and 8 g. of magnesium turnings), at −50°. The reaction mixture was allowed to come to room temperature at which point it became so viscous that additional solvent was added in order to continue stirring. Following hydrolysis and rectification, there was obtained 40 g. of material, b.p. 94–95°. Both the infrared spectrum and analytical data indicated that the alcohol was contaminated with a small amount of tetrahydrofuran, and it was found necessary to isolate the alcohol as the 3,5-dinitrobenzoate ester, m.p. 106–107°. The ester was found to react with ethanol and was recrystallized from petroleum ether and benzene. The conversion obtained in this manner represents 33% of the theoretical.

Anal. Calcd. for $C_{14}H_4O_6N_2F_{14}$: C, 29.9; H, 0.8. Found: C, 30.3; H, 0.98.

Reaction of the Grignard Reagent with 1,1,1-Trifluoro-2-propanone.—1,1,1-Trifluoro-2-propanone, 25 g. (0.25 mole), was added slowly to the Grignard reagent and the products were treated as previously described (the techniques of the reaction are such that it is inconvenient to add the Grignard reagent to 1,1,1-trifluoro-2-propanone). Distillation of the reaction mixture resulted in sublimation of a solid which, recrystallized from a mixture of benzene and petroleum ether, melted sharply at 93–94°. There are indications that this material is a polymer of 1,1,1-trifluoro-2-propanone.

Anal. Calcd. for $C_3H_3F_3O$: C, 32.1; H, 2.67. Found: C, 30.5; H, 2.63.

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(1) A. L. Henne and W. C. Francis, THIS JOURNAL, **73**, 3518 (1951).

(2) A. L. Henne and W. C. Frances, private communication.

(3) R. N. Haszeldine, *Nature*, **167**, 139 (1951).

(4) M. Hauptschein and A. V. Grosse, THIS JOURNAL, **73**, 2461 (1951).

(5) E. T. McBee, O. R. Pierce and M. C. Chen, private communication.

The Chemistry of Scandium. IV. The Structure of Scandium Oxinate

BY L. POKRAS, M. KILPATRICK AND P. M. BERNAYS

RECEIVED AUGUST 13, 1952

In a recent paper[1] on the 8-hydroxyquinoline compound of scandium[2] it was noted that, as in the cases of the analogous thorium, uranium and plutonium derivatives, the compound includes an "extra" molecule of oxine. For such compounds it is difficult to understand the nature of the chemical binding between the expected normal oxinate and the "extra" oxine molecule. The

(1) L. Pokras and P. M. Bernays, THIS JOURNAL, **73**, 7 (1951).

(2) The formula of the 8-hydroxyquinoline compound, $Sc(C_9H_6ON)_3 \cdot C_9H_7ON$, is abbreviated as $Sc(On)_3 \cdot HOn$; 8-hydroxyquinoline or oxine is written as HOn.

following new data lead us to believe that the "extra" molecule is bound merely by weak lattice forces and that the scandium compound is a lattice compound, capable of existence only in the solid state, and similar to Cs_3CoCl_5 and $(NH_4)_3ZrF_7$ discussed by Emeléus and Anderson.[3]

Experimental

The toluene employed as solvent was reagent grade, purified by distillation through a 12 to 15 theoretical plate column. The oxine was purified by double sublimation and contained less than 0.1% total impurities when so prepared. The scandium oxinate was prepared as described previously.[1]

Results and Discussion

Solutions of pure oxine in toluene from $1.41_4 \times 10^{-3}$ to 4.39×10^{-5} mole per liter of toluene at 25° were studied in a Beckman DU spectrophotometer equipped with a thermostated cell compartment. Appreciable absorption was found only in the region 280–400 mμ, with a band maximum at 317 mμ and molar extinction coefficient of 2490 at the band maximum.[4] In this concentration range, Beer's law is obeyed.

Similar studies of the absorption of pure $Sc(On)_3 \cdot HOn$ in toluene[5] indicated absorption maxima at 375 and 317 mμ. In solutions ranging from 2.36 to 0.589×10^{-4} molar in $Sc(On)_3 \cdot HOn$, Beer's law is not obeyed; the apparent molar extinction coefficient varied regularly from 5200 to 3820 at 375 mμ and from 7775 to 8340 at 317 mμ.

Additional studies were then made of the absorption of systems containing both HOn and $Sc(On)_3 \cdot HOn$. In one series of studies, seven solutions with constant $ScOn_3 \cdot HOn$ concentration and varying concentrations of added free HOn were examined. A second series of studies consisted of six systems with a fixed concentration of total oxine and oxinate; and varying scandium concentrations. Analysis of the resulting data[6] clearly indicated that there was no dissociation equilibrium in the system of the type: $Sc(On)_3 \cdot HOn \rightleftarrows ScOn_3 + HOn$. On the basis of the spectrophotometric data, $Sc(On)_3 \cdot HOn$ is either completely undissociated, or else completely dissociated in toluene; however, it is not possible to determine from this evidence which is the case.

The apparent molecular weight of the $Sc(On)_3 \cdot HOn$ in benzene was then determined, by freezing point depression, to be 330 ± 60. Since the calculated molecular weight of the compound is 622 the solutions must contain two particles per molecule and it is apparent that the substance must be completely dissociated into $Sc(On)_3$ and free HOn in benzene and toluene.

It seems reasonable that the energy of solvation of the scandium oxinate in toluene and benzene is quite small, probably less than 1 kcal. per mole. The binding cannot be either covalent or ionic because the compound is completely dissociated in these solvents and because such bond energies would have to be of the order of 30 to 50 kcal. per mole. It is difficult to see how solvation could account for the large energies required to dissociate either an ionic or covalent bond, or any bond of intermediate character. It follows that the binding can only be by weak lattice forces in the molecular crystal.

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(3) H. J. Emeléus and J. S. Anderson, "Modern Aspects of Inorganic Chemistry," D. Van Nostrand Co., Inc., New York, N. Y., 1944, pp. 80–81.

(4) The absorption of the solvent becomes too large below 280 mμ to permit measurements at shorter wave lengths.

(5) It should be noted that these solutions, like solutions of gallium and thallium(III) oxinates recently reported by Moeller and Cohen, *Anal. Chem.*, **22**, 686 (1950), are subject to slow photochemical decomposition. In diffuse light this phenomenon does not interfere seriously with the validity of the measurements if they are carried out within a few hours after preparation of the solutions.

(6) L. Pokras, "The Chemistry of Scandium," Ph.D. dissertation, Illinois Institute of Technology, 1952, pp. 68–80.

Diffusion of Hydrocarbon Vapors into Polyisobutylene. II[1]

BY S. PRAGER, E. BAGLEY AND F. A. LONG

RECEIVED NOVEMBER 8, 1952

Previous studies[2] of the rates of diffusion of the vapors of several hydrocarbons into polyisobutylene have been extended to higher and lower temperatures in order to determine the temperature coefficients for the diffusion and especially to determine variations in the energy of activation with size and shape of the diffusing molecule. The studies at 35° showed that the diffusion obeyed Fick's law (with the usual assumption of equilibrium concentration of vapor at the polymer surface) but with a concentration dependent diffusion coefficient. Furthermore, the magnitude of the diffusion coefficient at a given concentration depended on the size and particularly on the shape of the diffusing species.

Similar studies have now been made at 25 and 46.5° with the five hydrocarbons: *n*-butane, *n*-pentane, isobutane, isopentane and neopentane. The experimental procedures and materials were the same as used previously,[2] as was the method of evaluation of the diffusion coefficients from sorption and desorption data at various pressures. As at 35°, the diffusion coefficients at the other temperatures increased exponentially with concentration, following the equation

$$\bar{D} = \bar{D}_0 e^{AC} \qquad (1)$$

where $\bar{D}$ is the integral diffusion coefficient, C is concentration expressed as grams of hydrocarbon per gram of dry polymer and $\bar{D}_0$ and A are constants characteristic of a given hydrocarbon. All of these studies were made in the concentration range of from $C = 0$ to $C = 0.1$ g. of hydrocarbon per gram of polymer.

Table I gives values of the parameters $\bar{D}_0$ and A for the five hydrocarbons at the three temperatures, 25, 35 and 46.5°. Also included are values of V_m, the molar volume of the hydrocarbons at 25°.[3]

It is seen that at each temperature the values of $\bar{D}_0$, the diffusion coefficient at zero concentration,

(1) Research supported by Army Ordnance.

(2) S. Prager and F. A. Long, THIS JOURNAL, **73**, 4072 (1951).

(3) U. S. Nat. Bureau of Standards, API Res. Project 44, Properties of Hydrocarbons.

TABLE I

VALUES OF $\bar{D}_0$ AND A IN EQUATION (1)

Hydrocarbon	V_m, ml./mole	Temp., °C.	$D_0 \times 10^9$ (cm.^{2} sec.$^{-1}$)	A
n-Butane	101.4	25	1.17	28.0
		35	3.29	25.8
		46.5	7.54	22.8
Isobutane	105.5	25	0.53	28.8
		35	1.46	23.6
		46.5	3.75	19.0
n-Pentane	116.1	25	1.08	25.8
		35	2.59	24.7
		46.5	6.55	22.0
Isopentane	117.4	25	0.47	26.6
		35	1.34	22.5
		46.5	3.60	18.8
Neopentane	122.1	25	0.20	17.2
		35	0.60	14.5
		46.5	1.26	16.7

decrease from the smaller to the larger hydrocarbons. However, it is also evident that $\bar{D}_0$ is actually more influenced by the amount of branching than by the molar volume. Somewhat similar results have recently been reported by Park[4] for diffusion of various small molecules into polystyrene.

The temperature coefficient data fit the Arrhenius equation, $\bar{D} = B \exp(\Delta E^*/RT)$, since plots of log $\bar{D}$, for diffusion coefficients at a given concentration, *versus* $1/T$ give straight lines. Values of the Arrhenius parameters for $\bar{D}_0$ are given in Table II. As might be expected in view of the comparatively small variation in $\bar{D}_0$ with hydrocarbon, the values of the energy of activation do not vary widely, in fact by not much more than the estimated experimental error of ±0.5 kcal. (±1 kcal. for neopentane). However, there does appear to be a consistent trend in that ΔE^* values are lowest for the straight chain hydrocarbons and larger for the branched ones. These results show clearly that the diffusion is an activated process and are consistent with the notion that the slow step is formation of a hole in the polymer network.[2] However it should be noted that the variation of ΔE^* is surprisingly small in view of the considerable differences in the molar volumes and particularly in the minimal cross sectional areas of the molecules.

TABLE II

ARRHENIUS PARAMETERS FOR D_0 VALUES (CM.^{2} SEC.$^{-1}$)

Hydrocarbon	$10^9 D_0$, 35°	log B	ΔE^*, kcal.
n-Butane	3.3	3.4	16.7
Isobutane	1.5	3.6	17.5
n-Pentane	2.6	2.8	16.0
Isopentane	1.3	4.0	18.1
Neopentane	0.6	3.5	18

Values of energies of activation to compare with the above are available for polystyrene and polyvinyl acetate. For polystyrene, data are given by Park[5] for diffusion of methyl iodide (V_m = 62), methylene chloride (V_m = 63) and chloroform (V_m = 80). The calculated energies of activation vary with small molecule type and concentration and range from 14 to 27 kcal./mole. For polyvinyl acetate, values are available for acetone[6] (V_m = 73), propyl alcohol[7] (V_m = 75) and benzene[7] (V_m = 89 ml./mole).[7] For these three species, the energies of activation at zero concentration are 39, 41 and 37 kcal. per mole, respectively. Thus for diffusion into the two non-polar polymers the energies of activation are much lower than for the polar polyvinylacetate. This is the expected result since it implies that hole formation is considerably more difficult in a polar polymer.

(4) G. S. Park, *Trans. Faraday Soc.*, **47**, 1007 (1951).

(5) G. S. Park, *ibid.*, **46**, 684 (1950).

(6) R. J. Kokes, F. A. Long and J. L. Hoard, *J. Chem. Phys.*, **20**, 1711 (1952).

(7) R. J. Kokes, unpublished work.

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Irradiation of Liquid Ammonia[1]

BY RALPH ROBERTS[2] AND AUGUSTINE O. ALLEN

RECEIVED OCTOBER 10, 1952

Considerable evidence has been presented which has led to the concept of the existence of free electrons in alkali metal ammonia solutions.[3] Mass spectral data[4] indicate that ionization of ammonia to $NH_3^+ + e^-$ occurs more readily than any of the other possible ionization processes. Ionization along the path of the high energy bombarding ray has been postulated as one of the initial processes in the radiation effects of gamma and cathode rays. The above evidence led to an attempt to ascertain whether or not stabilized free electrons are formed by the high energy irradiation of liquid ammonia.

The ammonia was purified by distillation from a potassium solution in a suitable vacuum line. The sample for irradiation was collected in a conductivity cell with bright platinum electrodes. This was maintained at −70 to −73° by using chilled acetone inside the cell holder and Dry Ice external to this. The holder was designed so that the thin wall of the cell could be directly irradiated with the cathode ray beam. The source of radiation was a 2-Mev. electrostatic generator constructed by the High Voltage Engineering Corporation, which can be operated to produce either 2-Mev. cathode rays or X-rays. The cell dimensions were such that the cathode ray beam did not penetrate to ammonia as far as the vicinity of the electrodes. In X-ray irradiations the entire cell was exposed. The cell constant was determined by comparison of the resistance of conductivity water in the cell with that observed in a cell with a known cell constant. A 1000 cycle a.c. bridge with earphones or cathode ray oscillograph was used to measure the resistance of the liquid ammonia. The experimental results are shown in Table I.

The data in Table I show no evidence for the formation of conducting species during the irradiation. Even though the ammonia used had a lower specific resistance than the literature value[3a] the impurity, in equivalents of alkali metal ion, was between 10^{-7} and 10^{-8} mole per liter. A change in conductivity equivalent to a concentra-

(1) Research carried out under the auspices of the Atomic Energy Commission.

(2) Office of Naval Research, Washington 25, D. C.

(3) (a) C. A. Kraus, THIS JOURNAL, **36**, 864 (1914); (b) S. Freed and N. Sugarman, *J. Chem. Phys.*, **14**, 295 (1946); (c) C. A. Hutchison and R. C. Pastor, *Phys. Rev.*, **81**, 282 (1951).

(4) M. M. Mann, A. Hustrulid and J. T. Tate, *Phys. Rev.*, **58**, 346 (1940).

TABLE I

CONDUCTIVITY OF IRRADIATED LIQUID AMMONIA

Volume NH_3, 8.3 ml.

Exposure, sec.	Dark time, sec.	Target current, μa.	Roentgens[a] × 10^{-7}	Sp. resist × 10^6	r./μa.-sec. × 10^{-6}
Sample 3, temperature −74°; 2 Mev. cathode rays					
0	..	..		1.50	
65	..	3.4	1.8	1.50[b]	0.68
...	30	..	...	1.50	..
...	65	..	...	1.50	..
30	..	10.0	2.4	...	.80
150	..	3.5	4.3	1.45[b]	.82
120	..	3.6	3.5	...	.81

Total exposure time, min.	Current, μa.	Roentgens total	Sp. resist × 10^3
Sample 4, temperature −75° to −72°; 2 Mev. X-rays			
0	...	0	510
2	100	6 × 10^3	490[b]
5	100	1.5 × 10^4	450[b]
Off 5	...	.....	450
6	100	1.8 × 10^4	460[b]
8	100	2.5 × 10^4	...
8′20″	...	.....	460
Off 4	...	.....	460

[a] Dose calculated assuming only one-half ammonia irradiated. [b] Measurement made during irradiation.

tion of about 3 × 10^{-9} mole per liter of alkali metal or free electron in liquid ammonia could have been detected. On the basis of the data, no evidence was obtained for the formation of stabilized free electrons during the irradiation of liquid ammonia under the experimental conditions used.

Acknowledgment.—One of the authors (R. Roberts) wishes to acknowledge the assistance of the Office of Naval Research and Brookhaven National Laboratory which made the conducting of this research possible.

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The Effect of Esterification on Anticholinesterases as Determined by Three Different Enzymes

BY HENRY TAUBER AND EDWARD L. PETIT

RECEIVED NOVEMBER 8, 1952

The preparation of 50 phosphonic and phosphinic acids has been described recently from our laboratory.[1] These compounds were examined for their anti-plasma cholinesterase activity.[2] Several of the compounds were found to be quite active. A few of the acids were esterified. Most of the esters were much more active against human plasma cholinesterase than the free acids. It is desirable for the development of insecticides to examine the action of anticholinesterases on enzymes of different species. In the present experiments we subjected our most active compounds to a comparative study using three different enzymes, human plasma cholinesterase, pig brain acetylcholinesterase and fly brain acetylcholinesterase. The effect of the esters on the cholinesterase activity of the three different soluble enzyme preparations has also been tested.

Methods and Materials.—The human plasma cholinesterase was the same as in our previous work.[2] The method for the preparation of soluble pig brain acetylcholinesterase has been described recently.[3] A similar procedure was employed for the preparation of acetylcholinesterase from the heads of the house fly (*Musca domestica* L.). An activator buffer–salt solution[3] was used in conjunction with the pig brain and fly brain acetylcholinesterase but not with the human plasma cholinesterase. Details concerning the enzyme inhibitor experiments have been described previously.[2,3] Residual acetylcholine was analyzed by Hestrin's[4] method using Klett–Summerson photoelectric colorimeter.

Inhibition of Three Different Cholinesterases.—It may be seen in Table I that our most active compounds are all

TABLE I

THE EFFECT OF ESTERIFICATION ON ANTICHOLINESTERASES AS MEASURED BY THREE DIFFERENT ENZYMES

Compound	I_{50},[a] moles/l. Plasma ChE	Brain AChE	Fly AChE
(*o*-BrC_6H_4)$C_6H_5PO_2H$	6 × 10^{-6}	7 × 10^{-3}	>5 × 10^{-3}
(*o*-BrC_6H_4)$C_6H_5PO_2CH(CH_3)_2$	1 × 10^{-6}	2.5 × 10^{-4}	2.5 × 10^{-6}
(*o*-BrC_6H_4)$C_6H_5PO_2C_2H_5$	1 × 10^{-5}	2 × 10^{-4}	5 × 10^{-5}
(*o*-BrC_6H_4)$C_6H_5PO_2CH_3$	8 × 10^{-5}	3.1 × 10^{-3}	>1 × 10^{-3}
(*o*-BrC_6H_4)$_2PO_2H$	1 × 10^{-4}	5 × 10^{-3}	>5 × 10^{-3}
(*o*-BrC_6H_4)$_2PO_2C_2H_5$	3 × 10^{-5}	2.5 × 10^{-5}	2 × 10^{-5}
o-$BrC_6H_4PO_3H_2$	4 × 10^{-3}	>5 × 10^{-3}	>5 × 10^{-3}
o-$BrC_6H_4PO(OC_2H_5)_2$	1 × 10^{-5}	1.25 × 10^{-3}	1 × 10^{-3}

[a] The I_{50} values (concentrations required for 50% inhibition) in this table were obtained from graphs in which % inhibition was plotted against the logarithm of the molar concentration of the compounds.

ortho-halogen derivatives. The *m*-halogen derivatives were less active, while the *p*-substituted compounds had no activity. The meta and para compounds are not included in Table I. It may be seen that esterification considerably increased the inhibitory power of the free acids in most instances. The isopropyl ester of (*o*-bromophenyl)-phenylphosphinic acid was more inhibitory than its ethyl ester and methyl ester. Concerning the plasma enzyme the ethyl ester of bis-(*o*-bromophenyl)-phosphinic acid was about 33 times more inhibitory than the free acid and the ethyl ester of *o*-bromobenzenephosphonic acid was 400 times more active than the free acid. When the pig brain enzyme was employed the ethyl ester of bis-(*o*-bromophenyl)-phosphinic acid was 200 times more inhibitory than the free acid and when the fly brain enzyme was tested the ester was at least 250 times more active than the free acid.

Among the 3 enzymes human plasma cholinesterase is much more readily inhibited by all compounds with the exception of ethyl ester of (*o*-bromophenyl)-phenylphosphinic acid, than the pig brain and fly brain acetylcholinesterase. This is not surprising since the plasma cholinesterase and the two brain enzymes belong to 2 different groups of enzymes.

Acknowledgments.—The authors are grateful to Drs. G. O. Doak and L. D. Freedman for the phosphorus compounds.

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(2) L. D. Freedman, H. Tauber, G. O. Doak and H. J. Magnuson, *ibid.*, in press.

(3) H. Tauber, *ibid.*, **75**, 326 (1953).

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Preparation of a Cyclopentenone by the Stobbe Condensation

BY D. L. TURNER

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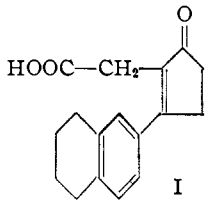
The Stobbe condensation with two δ-keto-esters has been shown to give substituted cyclohexen-

ones.[1,2] A similar reaction has now been observed with a γ-keto-ester. The crude Stobbe half-ester mixture from methyl β-(5,6,7,8-tetrahydro-2-naphthoyl)-propionate could not be purified because there was decomposition in an attempted vacuum distillation. It was hydrolyzed with alcoholic potash to give the cyclized product, 3-(5,6,7,8-tetrahydro-2-naphthyl)-2-cyclopenten-1-one-2-acetic acid (I), in 40% yield.

The structure of this cyclopentenone was easily demonstrated by preparing the same product from 2-acetyl-5,6,7,8-tetrahydronaphthalene by an established method.[3,4] The initial product of the Stobbe condensation was probably a 2-carbomethoxycyclopenten-1-one which lost its carbomethoxy group on hydrolysis.

The Stobbe condensation is the better of the two methods of preparation described.



I

Experimental

Furfurylidene-2-acetyl-5,6,7,8-tetrahydronaphthalene.—To 260 g. of 2-acetyltetrahydronaphthalene[5] in 600 ml. of ethanol and 124 ml. of furfural, was added 10 ml. of 45% aqueous potassium hydroxide solution. After standing overnight, the product was filtered; yield 350 g., m.p. 65–68°. A sample was recrystallized from ethanol, m.p. 65–66°.

Anal. Calcd. for $C_{17}H_{16}O_2$: C, 80.92; H, 6.39. Found: C, 80.87; H, 6.30.

ε-(5,6,7,8-Tetrahydro-2-naphthoyl)-homolevulinic Acid.—Treatment of 600 g. of the preceding with 7200 ml. of ethanol and 1800 ml. of concentrated hydrochloric acid followed by repeated extraction with a mixture of 3600 ml. of concentrated hydrochloric acid, 3600 ml. of acetic acid and 7200 ml. of water in the usual manner[3,4] gave 187 g. of the diketo acid (25%). A sample was recrystallized from ether–pentane, m.p. 114.5–115°.

Anal. Calcd. for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 70.95; H, 6.99.

3-(5,6,7,8-Tetrahydro-2-naphthyl)-2-cyclopenten-1-one-2-acetic Acid.—(a) This was prepared in the usual manner[3,4] from the preceding in 95% yield. The product was recrystallized from chloroform and then from ether, m.p. 129–130°.

Anal. Calcd. for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.32; H, 6.65.

The oxime of this keto-acid was prepared in pyridine–ethanol and recrystallized from ethyl acetate, m.p. 160–161° (dec.).

Anal. Calcd. for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71. Found: C, 71.55; H, 6.70.

The methyl ester made with diazomethane in ether was crystallized from ethanol, m.p. 88–89°.

Anal. Calcd. for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 75.72; H, 7.00.

(b) Methyl β-(5,6,7,8-tetrahydro-2-naphthoyl)-propionate was prepared by the esterification of the acid[6] using the method of Clinton and Laskowski.[7] The ester has been described by Newman and Zahm.[5] The ester (246 g.) dissolved in 292 g. of dimethyl succinate was added to a refluxing solution of 52 g. of potassium in 900 ml. of dry *t*-butyl alcohol in an atmosphere of nitrogen. A solid potassium salt separated immediately. The mixture was kept in an oil-bath at 110–130° for 30 minutes, cooled, and worked up by the usual method.[8] The acidic fraction weighed 325 g. (90%).

A 14-g. sample was dissolved in 100 ml. of ethanol containing 15 ml. of 45% aqueous potassium hydroxide. The solution was heated on the steam-bath. Water was added (50 ml.) to dissolve the precipitated salt and heating was continued for 30 minutes. The solution was cooled, acidified with dilute hydrochloric acid and extracted with ether. The ethereal solution was treated in the usual manner and the ether was removed. The residue was crystallized from chloroform–pentane giving 4.7 g. (45%), m.p. 129–130° undepressed on admixture with the preparation of (a) above. A repetition of the hydrolysis on a larger scale (116 g.) gave 36 g. of crude product and 25 g. of recrystallized material (m.p. 129–130°). An additional 14 g. (m.p. 128–130°) was recovered by treatment of the mother liquor with Girard Reagent T, followed by recrystallization of the ketonic fraction from chloroform.

Anal. Calcd. for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.51, 75.44; H, 6.63, 6.65.

The oxime, made as in (a) and crystallized from ethyl acetate had m.p. 161–162° (dec.) undepressed on admixture with the oxime of (a).

Anal. Calcd. for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71. Found: C, 71.63; H, 6.81.

The methyl ester was made with diazomethane and crystallized from ethanol, m.p. 87–89° undepressed on admixture with the ester of (a).

Anal. Calcd. for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 76.02; H, 7.05.

Acknowledgment.—I wish to thank Miss Ruth Horcher for technical assistance.

(1) D. L. Turner, THIS JOURNAL, **73**, 1284 (1951).
(2) D. L. Turner, *ibid.*, **73**, 3017 (1951).
(3) R. Robinson, *J. Chem. Soc.*, 1390 (1938).
(4) D. L. Turner, THIS JOURNAL, **71**, 612 (1949).
(5) M. S. Newman and H. V. Zahm, *ibid.*, **65**, 1097 (1943).
(6) L. F. Fieser and W. G. Dauben, *ibid.*, **70**, 3197 (1948).
(7) R. O. Clinton and S. Laskowski, *ibid.*, **70**, 3135 (1948).
(8) W. S. Johnson, A. Goldman and W. P. Schneider, *ibid.*, **67**, 1357 (1945).

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Methylpentaerythrityl Ether

BY S. WAWZONEK AND J. P. HENRY[1]

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In the formation of the methyl and dimethyl ethers of pentaerythritol by the Tollens condensation of acetaldehyde and formaldehyde in 50% methanol, β-methoxypropionaldehyde has been postulated as an intermediate.[2] This assumption has now been verified by the preparation of the methyl ether of pentaerythritol using β-methoxypropionaldehyde in the Tollens condensation in place of the acetaldehyde. The similar yield of this ether (13.4%) to that (11.4%) obtained from the condensation using acetaldehyde indicates that β-methoxypropionaldehyde is partly dissociated into acrolein and methanol in the Tollens condensation. This behavior is consistent with the mechanism proposed.[2]

Experimental[3]

β-Methoxypropionaldehyde[4] was prepared by adding acrolein (56.0 g.) to a solution of sodium methoxide (from 0.4 g. of sodium) in absolute methanol (150 ml.) at 0° in the course of three hours and allowing the resulting solution to

(1) Abstracted in part from the M.S. thesis of J. P. Henry, June, 1948.
(2) S. Wawzonek and D. A. Rees, THIS JOURNAL, **70**, 2433 (1948).
(3) Melting points and boiling points are not corrected.
(4) M. Heyse, German Patent 554,946; *C. A.*, **26**, 5964 (1932).

stir further for three hours at −5°. The product was not isolated but was added to a suspension of paraformaldehyde (180 g.) in methanol (100 ml.) and water (250 ml.). This mixture was treated with calcium oxide and the products isolated in a manner similar to that reported previously.[2] Fractionation of the propionates gave the tripropionate of methylpentaerythrityl ether (42.5 g.), b.p. 170–178° at 7 mm., $n^{25}D$ 1.4423. Wawzonek and Rees[2] reported a boiling point of 170–172° (6 mm.), $n^{25}D$ 1.4410.

Saponification of this ester (42.5 g.) in ethanol (25 ml.) with 6 *N* sodium hydroxide (250 ml.) by refluxing for four hours, followed by evaporation of the resulting solution, gave a solid which was extracted three times with 200-ml. portions of hot chloroform. Concentration and cooling of the chloroform gave methylpentaerythrityl ether (10.6 g.) (53%) melting at 70°. A mixture with an authentic sample[5] melted at the same point.

The ester fraction (15.3 g.) boiling below 170° (7 mm.) and that (18.7 g.) boiling at 178–200° (7 mm.), which no doubt contained the propionates of dimethylpentaerythrityl ether and pentaerythritol, respectively, were not investigated further.

(5) L. Orthner and Freyss, *Ann.*, **484**, 131 (1930).

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α-Maltosyl β-D-Fructofuranoside, a Trisaccharide Enzymically Synthesized from Sucrose[1]

BY JONATHAN W. WHITE, JR., AND JEANNE MAHER

RECEIVED OCTOBER 23, 1952

In the course of an investigation of the action of honey invertase upon sucrose with the objective of comparing such oligosaccharides as may be formed with those occurring in honey, six saccharides other than glucose, fructose and sucrose were demonstrated by paper chromatography.[2]

The synthesis of oligosaccharides during the action of yeast invertase upon sucrose has been described.[3] The most extensive data[4] describe five such compounds, two of which are non-reducing trisaccharides composed of two fructose and one glucose molecules. No data other than R_f values are given. deWhalley[5] has reported further data for one of the trisaccharides, confirming its monosaccharide composition and giving $[\alpha]^{22}D$ +26.61°. He named it kestose.

Since honey invertase differs from yeast invertase in its action on sucrose and other sugars[2,6] it might be expected that the intermediates formed in the action of these enzymes upon sucrose differ.

The principal trisaccharides formed by yeast invertase from sucrose contain two fructose and one glucose molecules[4,5]; the principal trisaccharide formed by honey invertase from sucrose contains two glucose and one fructose molecules.

This sugar has been isolated from a honey invertase digest of sucrose in a yield of 11% of the original weight of sucrose. The structure 4-(α-D-glucopyranosyl)-α-D-glucopyranosyl β-D-fructofuranoside is proposed for this compound. A more convenient name is α-maltosyl β-D-fructofuranoside. The proposed structure is based on the following reactions.

The trisaccharide is non-reducing to Fehling solution and gives glucose and fructose on hydrolysis. Yeast invertase splits the molecule only at the glucose–fructose linkage to give fructose and maltose, toward which the enzyme is inactive. This fixes the glucose–glucose linkage as α-1,4. Honey invertase, which synthesizes the sugar, also can degrade it completely to constituent monosaccharides. However, its mode of action is such that the terminal glucose is first split off, leaving sucrose. There is an accumulation of sucrose during the reaction, which eventually is hydrolyzed completely. This fixes the glucose–fructose linkage as that in sucrose, or β-D-fructofuranosyl α-D-glucopyranoside. Thus, linkages and stereochemical forms of the constituent monosaccharides in the trisaccharide are fixed by identification of maltose and sucrose as degradation products.

Experimental

Preparation of α-Maltosyl β-D-Fructoside.—A honey invertase concentrate was prepared from unheated 1948 fall flower honey by the procedure of Nelson and Cohn.[7] One ml. of the preparation (equivalent to the enzyme content of 32 g. of honey) inverted 0.86 g. of sucrose in 125 minutes at 26°, *p*H 5.8 in 10 ml. of 15% sucrose solution.

A solution of 8.35 g. of sucrose, 2 ml. of 2 *M* acetate buffer at *p*H 5.7 and 5.55 ml. of honey invertase was made to 50 ml. and allowed to stand 128 minutes at 26°. At this time 24% of the original sucrose remained. The solution was heated and subjected to chromatography on a 36 × 160 mm. carbon–diatomaceous earth column as described by Whistler and Durso.[8] Details of the separation are given elsewhere.[2] The fraction eluted with 50% ethanol (0.944 g.) contained all compounds higher than disaccharides, since it followed the 5% ethanol (disaccharide) fraction directly.

Paper chromatography of this fraction showed it to contain principally a non-reducing, ketose-containing material of R_S[9] 0.57 (solvent, butanol 3, pyridine 1, water 1.5)[10]. Small amounts of other materials were present whose migration on the papergram corresponded to that of disaccharides (R_S 1.00) and tetrasaccharides (R_S 0.26).

In a typical purification, 160 mg. of the crude material was freed of these contaminants by chromatography on a powdered cellulose column essentially as described by Hough, *et al.*[11] The solvent used was butanol 41.6, ethanol 47.6, water, 22.5 parts by volume, a single-phase solvent which gives relatively rapid movement of trisaccharides. Samples from the 1-ml. eluate fractions were chromatographed on paper to locate the constituents. The eluate fractions containing only the trisaccharide were combined to yield 123 mg. of material. Since the product has not been crystallized, material from several runs was evaporated and dried for analysis at a pressure of 1.6 mm. at 105° to constant weight. It had $[\alpha]^{25}D$ +121.8° (2.3% in water). No definite melting point was obtained for the amorphous material.

α-Maltosyl β-D-Fructoside Hendecaacetate.—The trisaccharide (100 mg.) was treated with acetic anhydride in pyridine at room temperature by the procedure of Barker and Bourne.[12] The product was dried at pressure of 2 mm. at 60° to constant weight. It was not crystallized. It had $[\alpha]^{25}D$ +86.0° (1.2%, $CHCl_3$).

(1) Report of work carried out under the provisions of the Research and Marketing Act of 1946. Presented at the 122nd Meeting of the American Chemical Society, Division of Sugar Chemistry, Atlantic City, N. J., Sept. 16, 1952.

(2) J. W. White, Jr., and J. Maher, *Arch. Biochem. Biophys.*, in press.

(3) J. S. D. Bacon and J. Edelman, *ibid.*, **28**, 467 (1950); P. H. Blanchard and N. Albon, *ibid.*, **29**, 220 (1950); E. H. Fischer, L. Kohtes and J. Fellig, *Helv. Chim. Acta*, **34**, 1132 (1951).

(4) L. M. White and G. Secor, *Arch. Biochem. Biophys.*, **36**, 490 (1952).

(5) H. C. S. deWhalley, *Internat. Sugar J.*, **54**, 127 (1952).

(6) G. Gorbach and R. Schneiter, *Biochem. Z.*, **296**, 367 (1938).

(7) J. M. Nelson and D. J. Cohn, *J. Biol. Chem.*, **61**, 193 (1924).

(8) R. L. Whistler and D. F. Durso, THIS JOURNAL, **72**, 677 (1950).

(9) R_S is ratio of travel of spot to travel of sucrose on same paper.

(10) A. Jeanes, C. S. Wise and D. J. Dimler, *Anal. Chem.*, **23**, 415 (1951).

(11) L. Hough, J. K. N. Jones and W. H. Wadman, *J. Chem. Soc.*, 2511 (1949).

(12) S. A. Barker and E. J. Bourne, *ibid.*, 209 (1952).

Anal. Calcd. for $C_{40}H_{54}O_{27}$: C, 49.67; H, 5.63. Found: C, 49.40; H, 5.48.

Hydrolysis of α-Maltosyl β-D-Fructoside by Yeast Invertase.—The trisaccharide (15 mg.) was dissolved in 0.1 ml. of a 1% aqueous solution of Wallerstein Blue Label invertase.[13] After 180 minutes a sample was removed to paper, steamed and irrigated. All papergrams were irrigated downward with *n*-butanol 3, pyridine 1, water 1.5.[11] Two products were shown: a reducing, non-ketose-containing disaccharide (R_S 0.75) and fructose (R_S 1.51). For identification, 145.4 mg. of the trisaccharide was dissolved in 1 ml. of water to which was added 1 ml. of 1% Wallerstein invertase. After 45 minutes at 37° it was heated to boiling, cooled, filtered and the filtrate evaporated to dryness under reduced pressure. It was subjected to partition chromatography on a powdered cellulose–diatomaceous earth (2:1) column using as a solvent the upper phase of a mixture of butanol 4, ethanol 1, water 5.[14] The filtrate was collected in 1-ml. fractions. Fractions 60–80 contained fructose, fraction 75 a trace of glucose, and fractions 85–150 a disaccharide. These last fractions were combined and from them was obtained 92.8 mg. of the disaccharide, 95% of calcd. This material was reducing, contained no fructose, was not split by yeast invertase, was hydrolyzed to glucose by honey invertase, and could not be differentiated from maltose by paper chromatography. It was crystallized from aqueous ethanol; the X-ray powder diffraction pattern of the crystalline product agreed in all respects with that of an authentic sample of maltose hydrate. The disaccharide produced by yeast invertase from the trisaccharide was therefore maltose.

The monosaccharide could not be differentiated from fructose by paper chromatography with fructose and by reaction to naphthoresorcinol, TTC and benzidine reagents.

Hydrolysis of α-Maltosyl β-D-Fructoside by Honey Invertase.—The trisaccharide (15 mg.) was dissolved in 0.1 ml. of honey invertase solution. Samples were removed for paper chromatography at 10 and 180 minutes, steamed and irrigated. The papergram of the 10-minute reaction showed in addition to the original trisaccharide (R_S 0.59) a ketose-containing, non-reducing disaccharide (R_S 1.01) and glucose (R_S 1.36). Only glucose and fructose (R_S 1.56) were found on the papergram of the 180-minute reaction.

For identification of the intermediate disaccharide, 110 mg. of the trisaccharide dissolved in 0.77 ml. of a honey invertase preparation. The reaction was stopped by heating at 30 minutes, filtered, evaporated dry and the constituents separated by powdered cellulose column chromatography as above. Fractions 70–85 showed glucose, 80–105 the disaccharide, and 105–191 contained unreacted trisaccharide. The appropriate fractions were combined to yield 5.0 mg. of monosaccharide, 9.6 mg. of disaccharide and 63 mg. of unreacted maltosyl fructoside. Based upon trisaccharide which was not recovered, this is a 38% conversion to disaccharide.

The monosaccharide could not be distinguished from glucose by paper chromatography and reaction to spray reagents. The disaccharide was non-reducing, contained ketose, and travelled on the papergram with sucrose. It was crystallized by repeated evaporation from aqueous ethanol solution. The X-ray powder diffraction pattern of the crystalline disaccharide was identical in all respects with that of authentic sucrose.

When a solution of glucose and fructose is treated with the honey enzyme under these conditions, there is no reaction discernible by paper chromatography.

The intermediate disaccharide produced by action of honey invertase upon α-maltosyl β-D-fructofuranoside is therefore sucrose.

Another honey invertase hydrolysis of the trisaccharide was carried out under conditions which by preliminary experiments were found to produce a better yield of sucrose. Treatment of 145.8 mg. with 1 ml. of a honey invertase preparation and 0.3 ml. of 2 *M* acetate buffer of *p*H 4.05, was carried out at 25° for 2 hours. It was heated to inactivate the enzyme, filtered and subjected to partititon chromatography on the cellulose column. From the column 88.3 mg. of unreacted material was obtained, and also a fraction containing sucrose, glucose and a small amount of fructose. This latter fraction was analyzed for reducing sugar before and after inversion by dilute acid. It was found to contain 27.2 mg. of reducing sugar as glucose before hydrolysis and 62.0 mg. after hydrolysis. The increase, 34.8 mg., corresponds to 33.1 mg. of sucrose.

This is 85% of the theoretical yield of sucrose[15] from the 57.5 mg. of trisaccharide destroyed.

Mild Acid Hydrolysis of α-Maltosyl β-D-Fructoside.—The compound (15 mg.) was dissolved in 1.2 ml. of H_2O and 0.5 ml. of 5 *N* H_2SO_4 added. After heating to 70° it was allowed to stand 24 hours at room temperature. The acid was then neutralized with solid $BaCO_3$, filtered and evaporated dry. Paper chromatography showed that levulose was hydrolyzed from the trisaccharide, leaving maltose, the same disaccharide formed by yeast invertase. The greater sensitivity of the sucrose linkage to acid hydrolysis is well known.

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(13) Mention of trade names does not imply endorsement by the Department over similar products not mentioned.

(14) S. M. Partridge, *Nature*, **158**, 270 (1946).

(15) The remaining 15% of the sucrose was further hydrolyzed to glucose and fructose. Complete conversion of this portion would produce 6.2 mg. of invert sugar, which when added to the 20.6 mg. of glucose, from the hydrolysis of the trisaccharide would total 26.8 mg. of reducing sugar. Actually 27.2 mg. was found.

(16) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. Article not copyrighted.