mer of approximately the same inherent viscosity as that before the reduction.

A polymer which is produced in the first rapid reaction between hexamethylenedithiol and biallyl (inherent viscosity 0.472) has been isolated and oxidized with iodine to produce a product with a higher viscosity which resembles in all ways a product formed by the usual long polymerization process. Moreover, this polymer can be again reduced to give a product of lower inherent viscosity.

It is a significant fact that reduction of the higher molecular weight product does not reduce the viscosity enough to indicate that all material present after reduction is half of the original molecular weight. Neither does oxidation of a low viscosity polymer double the molecular weight, as a rule. This would suggest that not all the high molecular weight polyalkylene sulfide molecules contain a central disulfide linkage. Some termination of the polymerization reaction may involve dimerization of carbon free radical intermediates as was suggested earlier.[3]

Polyhexamethylene sulfides were also prepared from hexamethylenedithiol and biallyl with azo-bis-isobutyronitrile as the initiator. In 18 hours at 50° these polymers grew to an inherent viscosity of 0.5 to 0.65. These polymers could be oxidized with iodine to give polymers with an inherent viscosity of over 1.0. The unoxidized polymers were not reduced in viscosity when treated with zinc and acid in xylene solution. Hence they apparently still retain the mercaptan end groups.

Experimental

All inherent viscosities were determined on solutions of 0.20 g. of polymer in 50 ml. of chloroform at 25°.

Preparation of Polymers.—Polyhexamethylene sulfide polymers (inherent viscosity of 0.8 to 0.9) were prepared as described earlier[4] and also by initiating the reaction with azo-bis-isobutyronitrile. This initiator was used in the standard acetate buffered emulsions at *p*H 3.5 and the mixture tumbled at 50° for 18 hours. The ammonium persulfate, sodium bisulfite, cupric sulfate and *p-t*-butylcatechol used in the standard method were omitted and 0.03 g. of azo-bis-isobutyronitrile was introduced. The polymers were isolated as before. Polymers were obtained in 94–99% yield which had inherent viscosities of 0.5 to 0.65.

Reduction of High Molecular Weight Polyhexamethylene Sulfide Polymers.—One gram of persulfate initiated polymer (inherent viscosity 0.829) was dissolved in 150 ml. of xylene. Amalgamated zinc (about 30 g.) was added, stirring was started, the temperature was raised to 80° and then over a period of 12 to 18 hours 30 ml. of aqueous hydrochloric acid (one part of sp. gr. 1.19 hydrochloric acid to one part of water) was added at the rate of three to five drops per minute. After that time the mixture was cooled, filtered and poured into a large excess of cold methanol. The polymer isolated had an inherent viscosity of 0.537. Analytically its composition was unchanged. The melting point and appearance of the polymer was also essentially unchanged.

Oxidation of Low Molecular Weight Polyhexamethylene Sulfide Polymers.—One gram of persulfate initiated polymer (produced in the first five to eight minutes of reaction, inherent viscosity 0.472) was dissolved in 50 ml. of chloroform and to the solution was added about 0.2 g. of iodine. The solution was tumbled at 50° for about 24 hours, much of the solvent evaporated and the polymer isolated by pouring the residue into methanol. The product isolated had an inherent viscosity of 1.013 and in all respects appeared to be identical with a polymer produced in the usual long time polymerization.

Other Oxidation and Reduction Experiments.—In the following tables are collected the results of a number of oxidation and reduction experiments on a variety of polyhexamethylene sulfides.

TABLE I

REDUCTION AND REOXIDATION OF PERSULFATE INITIATED POLYHEXAMETHYLENE SULFIDES

Experiment no.	Inherent viscosity: Of original polymer	After zinc reduction	After reoxidation with I_2
3–4[a]	0.691	0.514	...
7–5	.801	.633	0.815
7–4	.829	.537	0.780
6–2	.921	.849	1.039

[a] The polymer used in experiment 3–4 had the following analysis: C, 62.31; H, 10.26; S, 27.67. After reduction with zinc the analysis was: C, 61.89; H, 10.13; S, 27.22. The calculated values of $[C_6H_{12}S]_x$ are C, 62.00; H, 10.41; S, 27.59.

TABLE II

AZO-BIS-ISOBUTYRONITRILE INITIATED POLYHEXAMETHYLENE SULFIDES

Experiment no.	Inherent viscosity: Original inherent viscosity	After oxidation with I_2	After subsequent reduction
12–9	0.617	...	0.605[a]
6–6	.657	0.812	.664
12–7	.507	1.295	.703
12–8	.507	1.194	....
6–7	.478	0.650	....

[a] This sample was reduced without intermediate oxidation.

NOYES CHEMICAL LABORATORY
UNIVERSITY OF ILLINOIS
URBANA, ILL.

(4) C. S. Marvel and G. Nowlin, THIS JOURNAL, **72**, 5026 (1950).

Some Xanthineacetic Acid Derivatives

BY FREEMAN H. MCMILLAN AND H. M. WUEST

RECEIVED DECEMBER 8, 1952

In continuation of our program in the search for new analeptic drugs[1] it was decided to prepare N,N-diethyltheophylline-7-acetamide and N,N-diethyltheobromine-1-acetamide. The preparation of these and some closely related compounds together with some observations concerning their chemical properties constitute the subject matter of this paper.

Theophylline-7-acetic acid was prepared as described in the literature.[2] This acid was converted by usual methods to the ethyl ester in 83% yield and to the acid chloride in 36% yield. Theophylline-7-acetamide was prepared by shaking a benzene solution of theophylline-7-acetyl chloride with ice and excess ammonium hydroxide. N,N-Diethyltheophylline-7-acetamide was not obtained by treatment of theophylline-7-acetyl chloride with excess diethylamine in benzene; this was prepared, however, by treatment of theophylline with N,N-diethylchloroacetamide in aqueous sodium hydroxide solution or, in better yield, in ethanolic sodium hydroxide solution.

As in the case of 2-(3-pyridazonyl)-acetic acid,[3] theophylline-7-acetic acid when refluxed with acetic anhydride and pyridine, gave off carbon dioxide

(1) For the previous paper on this topic see F. H. McMillan and J. A. King, THIS JOURNAL, **73**, 3165 (1951).

(2) E. Merck, O. Wolfes and E. Kornick, German Patent 352,980, March 20, 1922.

(3) J. A. King and F. H. McMillan, THIS JOURNAL, **74**, 3222 (1952).

and 7-acetonyltheophylline was isolated in 36% yield; this compound was characterized as a ketone by semicarbazone formation.

Theobromine-1-acetic acid was prepared by the same method[2] as was used to prepare theophylline-7-acetic acid, *viz.*, alkylation of the parent xanthine with sodium chloroacetate in aqueous sodium hydroxide although considerable unalkylated theobromine was recovered from this reaction and the yield was only 25%. In contrast to theophylline-7-acetic acid, theobromine-1-acetic acid did not give a readily isolatable acid chloride when treated with thionyl chloride; the ethyl ester, however, was formed in moderate yield in ethanol containing a little sulfuric acid.

Ethyl theobromine-1-acetate was treated with excess cold concentrated ammonium hydroxide; after three days of standing, however, no amide was formed and the ester was recovered almost quantitatively. Theobromine-1-acetamide was prepared in 34% yield by bubbling ammonia through molten theobromine-1-acetic acid at 280–290°. When this same technique was applied in an attempt to prepare N,N-diethyltheobromine-1-acetamide no reaction took place. Attempted alkylation of theobromine with N,N-diethylchloroacetamide in aqueous sodium hydroxide gave no homogeneous product; N,N-diethyltheobromine-1-acetamide was obtained, however, in poor yield (12%) by using absolute ethanol as the solvent and sodium ethoxide as the base.

When theobromine-1-acetic acid was refluxed with acetic anhydride and pyridine no carbon dioxide was evolved and the acid was recovered unchanged.

The more satisfactory alkylation of theophylline is in agreement with the conclusions of Biltz and Beck,[4] who stated that in xanthines the order of decreasing ease of alkylation of the nitrogens is 3 > 7 > 1. If one agrees with the above authors' conclusions that this sequence is also that of decreasing acidity of the hydrogen atoms, one has an explanation for the more ready reactivity of theophylline-7-acetic acid with acetic anhydride and pyridine. That nitrogen atom possessing the more labile hydrogen atom will also more easily facilitate carbanion formation on the methylene group of a corresponding acetic acid residue; it has been previously demonstrated[5] that ease of carbanion formation of the carbon adjacent to the carboxyl group is a controlling factor in the course of the decarboxylative acylation of carboxylic acids.

Preliminary pharmacological evaluation of these substances indicates that they do exhibit some central nervous stimulant activity.

Experimental[6,7]

Theophylline-7-acetyl Chloride.—A mixture of theophylline-7-acetic acid[2] (12.0 g., 0.05 mole) and thionyl chloride (100 ml.) was refluxed for one hour; the excess thionyl chloride was evaporated under vacuum leaving a reddish-brown residue which on crystallization from benzene (100 ml.) gave 4.7 g. (36%) of yellowish crystals which melted at 150–154° (dec.).

Anal. Calcd. for $C_9H_9N_4O_3Cl$: N, 21.83. Found: N, 21.64.

Theophylline-7-acetamide.—Crude theophylline-7-acetyl chloride (2 g., 0.008 mole) in benzene (80 ml.) was shaken with concentrated ammonium hydroxide (15 ml.) and ice for 15 minutes. Crystalline material separated from the mixture which after four crystallizations from water weighed 1.1 g. (58%) and melted at 272–273°.

Anal. Calcd. for $C_9H_{11}N_5O_3$: C, 45.56; H, 4.67; N, 29.53. Found: C, 45.71; H, 4.74; N, 29.27.

Ethyl Theophylline-7-acetate.—A mixture of theophylline-7-acetic acid (6.0 g., 0.025 mole) and absolute ethanol (100 ml.) containing a few drops of sulfuric acid was refluxed for 3.5 hours. The hot mixture was filtered to remove a little undissolved material; chilling the filtrate gave 5.5 g. (83%) of crystals melting at 138–139°. An analytical sample, after three crystallizations from water, melted at 143–144°.

Anal. Calcd. for $C_{11}H_{14}N_4O_4$: C, 49.62; H, 5.30; N, 21.06. Found: C, 49.89; H, 5.02; N, 21.12.

N,N-Diethyltheophylline-7-acetamide.—Theophylline (11.9 g., 0.06 mole) was added to a solution of sodium hydroxide (2.4 g., 0.06 mole) in water (280 ml.); this mixture was cooled to 5° and N,N-diethylchloroacetamide (9.0 g., 0.06 mole) was added dropwise, over a period of 15 minutes, with vigorous stirring. The temperature of the mixture was allowed to come to 25° and then the mixture was heated at reflux for two hours. On standing overnight at room temperature there were deposited crystals which, after two crystallizations from water, weighed 1.5 g. (9%) and melted at 186–187°.

Anal. Calcd. for $C_{13}H_{19}N_5O_3$: C, 53.23; H, 6.53; N, 23.90. Found: C, 53.49; H, 6.31; N, 23.94.

When this reaction was repeated in ethanol the yield was 5.0 g. (29%) melting at 182–183°.

7-Acetonyltheophylline.—A mixture of theophylline-7-acetic acid (7.1 g., 0.03 mole), acetic anhydride (30 ml.) and pyridine (30 ml.) was refluxed for one hour during which about 200 ml. of carbon dioxide was collected. The solution was evaporated to dryness under vacuum; the residue after two crystallizations from ethanol (50 ml.) gave 2.5 g. (36%) of crystals melting at 160–161°.

Anal. Calcd. for $C_{10}H_{12}N_4O_3$: C, 50.84; H, 5.12; N, 23.75. Found: C, 50.96; H, 4.93; N, 23.54.

A small sample of this ketone gave a semicarbazone which after crystallization from ethanol melted at 247–248° (dec.).

Anal. Calcd. for $C_{11}H_{15}N_7O_3$: N, 33.06. Found: N, 33.47.

Ethyl Theobromine-1-acetate.—A mixture of theobromine-1-acetic acid[2] (6.0 g., 0.025 mole) and absolute ethanol (100 ml.) containing a few drops of sulfuric acid was refluxed for 3.5 hours. The hot mixture was filtered to remove a little undissolved material; the filtrate on cooling deposited crystals which melted at 154–157° to an opaque melt. This material was suspended in water (25 ml.) and 2 *N* sodium hydroxide was added until the solution was distinctly alkaline; the resulting suspension was heated to boiling and water added (85–90 ml.) until everything dissolved. Chilling gave 3.3 g. (50%) of crystals which melted at 163–164.5°. An analytical sample after recrystallization from water melted at 165–166°.

Anal. Calcd. for $C_{11}H_{14}N_4O_4$: C, 49.62; H, 5.30; N, 21.06. Found: C, 49.72; H, 5.53; N, 21.11.

Theobromine-1-acetamide.—Theobromine-1-acetic acid (6.0 g., 0.025 mole) was placed in a 100-ml. flask immersed in a Wood's metal bath; the bath temperature was maintained at 290–295° while ammonia was bubbled through the molten acid for one hour. The cooled melt was crystallized from water (100 ml.) giving 2.0 g. (34%) of crystals which melted at 301–302° (dec.).

Anal. Calcd. for $C_9H_{11}N_5O_3$: C, 45.56; H, 4.67; N, 29.53. Found: C, 45.43; H, 4.55; N, 29.55.

N,N-Diethyltheobromine-1-acetamide.—To a solution of sodium (1.4 g., 0.06 mole) in ethanol (100 ml.) there was added theobromine (10.8 g., 0.06 mole) followed by dropwise addition of N,N-diethylchloroacetamide (9.0 g., 0.06 mole) at below 10°. The mixture was allowed to come to room temperature and was then heated at reflux for two hours. The hot solution was filtered and the filtrate evap-

(4) H. Biltz and A. Beck, *J. prakt. Chem.*, [2] **118**, 198 (1928).

(5) J. A. King and F. H. McMillan, THIS JOURNAL, **73**, 4911 (1951).

(6) Melting points are uncorrected.

(7) Microanalyses were carried out under the direction of Dr. F. A. Bühler of this Institute.

orated to dryness under vacuum leaving a residue which after two crystallizations from ethanol weighed 2.0 g. (12%) and melted at 210–211°.

Anal. Calcd. for $C_{13}H_{19}N_3O_3$: C, 53.23; H, 6.53; N, 23.90. Found: C, 53.58; H, 6.35; N, 23.87.

WARNER-CHILCOTT RESEARCH LABORATORIES
113 WEST 18TH STREET
NEW YORK 11, NEW YORK

Syntheses in the Indene Series[1]

BY JOHN KOO[2]

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In connection with a projected synthesis of colchicine analogs, various substituted indenes were prepared as model compounds. Attempts were made to introduce substituents which, by cyclization, might yield tricyclic systems. The present note describes the synthesis of some of those indene derivatives.

Veratraldehyde and piperonal were condensed with ethyl acetoacetate by an extension of Knoevenagel's method,[3] and the resulting benzylideneacetoacetic esters (Ia,b) hydrogenated to the benzylacetoacetic esters (IIa,b).[4] Acid-catalyzed cyclodehydration of IIa and IIb produced the indene esters IIIa and IIIb, in addition to small amounts of the corresponding carboxylic acids, which resulted from hydrolysis accompanying the cyclization. Analogously, veratrylacetone (IIc)[5] and veratrylacetophenone (IId)[6] were cyclized to the indene derivatives IIIc and IIId. The indene ester IIIa and the phenylindene IIId condensed with ethyl oxalate to form IVa and IVd in 85 and 76% yields, respectively, while the methylindene IIIc failed to yield an oxalyl derivative. Apparently, activation by an aryl group in the 3- or by an ester group in the 2-position is required for formation or sufficient resonance stabilization of the carbanion which must be an intermediate in the condensation with ethyl oxalate. Since IVa and IVd form enol acetates, it is believed that they exist, at least partly, in the tautomeric enolic forms (Va,d). Attempts to reduce the carbonyl group in IVa to a methylene group by catalytic hydrogenation with palladium–carbon or by chemical reduction with aluminum amalgam failed or yielded inseparable mixtures. It was possible, however, to hydrogenate the indene ester IIIa to the indane ester VIa in 77% yield.

Experimental[7]

Ethyl Veratrylideneacetoacetate (Ia).—A homogeneous mixture of 182.6 g. of veratraldehyde, 130 g. of ethyl acetoacetate and 70 ml. of benzene was refluxed with 3.4 g. of piperidine and 12.2 g. of glacial acetic acid. Water liberated in the reaction was collected in a moisture trap. The reaction was completed in two hours, at which time 25 ml. of water had been collected. The solution was then cooled, diluted with 300 ml. of ether, washed twice with 100 ml. each of very dilute acetic acid and once with water, and dried over magnesium sulfate. After removal of solvents, the product was distilled to yield 175 g. (63%) of a pale yellowish oil, b.p. 190–192° (1 mm.), which solidified after standing for two days and then melted at 75–81°.

Anal. Calcd. for $C_{15}H_{18}O_5$: C, 64.73; H, 6.25. Found: C, 64.60; H, 6.60.

Ethyl Piperonylideneacetoacetate (Ib).—This compound was obtained from piperonal in 62% yield by the procedure used for the preparation of Ia. The pale yellow oil, b.p. 179° (1.6 mm.), solidified on standing and remelted at 74–77°.

Anal. Calcd. for $C_{14}H_{14}O_5$: C, 64.11; H, 5.37. Found: C, 63.78; H, 5.49.

Ethyl Veratrylacetoacetate (IIa).—A solution of 139 g. of IIa in 150 ml. of ethyl acetate was hydrogenated with 9 g. of 5% palladium–carbon catalyst at room temperature and 45 lb. pressure for two hours. Removal of catalyst and solvent, followed by vacuum distillation, provided 100 g. (70%) of colorless oil, b.p. 169° (1 mm.).

Anal. Calcd. for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.27; H, 7.01.

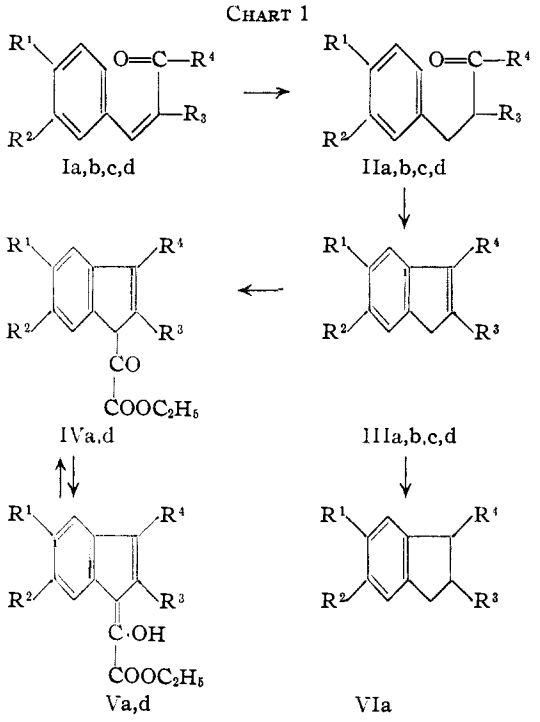
The 2,4-dinitrophenylhydrazone formed yellowish crystals (from dilute ethanol), m.p. 116–117°.

Anal. Calcd. for $C_{21}H_{24}O_8H_4$: C, 54.78; H, 5.28. Found: C, 54.74; H, 5.36.

Ethyl Piperonylacetoacetate (IIb).—Hydrogenation of Ib by the above procedure gave a 52% yield of colorless oil, b.p. 151–153° (0.8 mm.) (reported[4] 160–161° (4 mm.)).

Veratrylacetone (IIc).—This compound was similarly obtained in 83% yield by reducing 69 g. of veratrylideneacetone (Ic),[5,8] m.p. 84–86° (reported 91–92°,[5] 84–85°[8]), with 5 g. of palladium–carbon catalyst in 150 ml. of glacial acetic acid for 35 minutes. The colorless material had b.p. 127–129° (0.5 mm.) and m.p. 53–56° (reported[5] b.p. 181° (14 mm.), m.p. 55°).

CHART 1



Series a: $R^1 = R^2 = OCH_3$; $R^3 = CO_2C_2H_5$; $R^4 = CH_3$
Series b: $R^1 = R^2 = -OCH_2O-$; $R^3 = CO_2C_2H_5$; $R^4 = CH_3$
Series c: $R^1 = R^2 = OCH_3$; $R^3 = H$; $R^4 = CH_3$
Series d: $R^1 = R^2 = OCH_3$; $R^3 = H$; $R^4 = C_6H_5$

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(2) American Cancer Society Postdoctoral Fellow, 1948–1950; Special Research Fellow of the National Cancer Institute, National Institutes of Health.

(3) E. Knoevenagel, *Ber.*, **29**, 172 (1896); **31**, 730 (1898).

(4) R. H. Barry, A. M. Mattocks and W. H. Hartung, THIS JOURNAL, **70**, 693 (1948), prepared IIb from piperonal *via* piperonyl alcohol and piperonyl chloride.

(5) A. Kaufmann and R. Radosević, *Ber.*, **49**, 675 (1916).

(6) P. Pfeiffer, E. Kalckbrenner, W. Kunze and K. Levin, *J. prakt. Chem.*, [2] **119**, 109 (1928).

(7) Melting points are corrected and boiling points uncorrected. Analyses were carried out by Mrs. S. M. Woods of the University of Pennsylvania, and by Dr. W. C. Alford and his associates of the National Institutes of Health.

(8) C. F. Van Duin, *Rec. trav. chim.*, **45**, 345 (1926).