THE JOURNAL OF Organic Chemistry®

Volume 24, Number 8

August 31, 1959

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF SYRACUSE UNIVERSITY]

Condensation of Thiophenols and Formaldehyde with Some Aromatic Amines

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Received September 25, 1958

N-Arylaminomethyl aryl sulfides and 1,3,5-triaryl-1,5-dithia-3-azapentanes have been prepared by condensing primary aromatic amines with formaldehyde and thiophenols. *N*-Methylanilines condense with formaldehyde and thiophenols to form *N*-methyl-*N*-arylaminomethyl aryl sulfides.

Two arylaminoethyl aryl sulfides were prepared by condensing β-chloroethylaniline with the sodium salt of the thiophenol.

Basicities of these arylaminoalkyl aryl sulfides have been related to (a) the presence of electrophilic substituents attached to the aryl groups and (b) the number of carbon atoms separating the nitrogen and sulfur atoms.

Recently Grillot *et al.*[1] have demonstrated that the thiophenols condense with secondary aliphatic amines and formaldehyde to form dialkylaminomethyl aryl sulfides similar in structure to the dialkylaminomethyl alkyl sulfides prepared by McLeod and Robinson[2] by condensing aliphatic mercaptans with aliphatic amines and formaldehyde. The formation of these aminomethyl aryl sulfides was somewhat surprising, since phenols condense with secondary aliphatic amines and formaldehyde to form ortho and para substituted dialkylaminomethylphenols.[3]

Although aromatic amines generally react with more sluggishness in the Mannich reaction than the corresponding aliphatic amines, *N*-methylaniline, *N*-methyl-*p*-anisidine, and *N*-methyl-*p*-nitroaniline react with thiophenols and formaldehyde according to the following equation:

$$MeNHAr + HCHO + Ar'SH \longrightarrow Ar(Me)NCH_2SAr' + H_2O$$

to give moderately stable crystalline *N*-methyl-*N*-arylaminomethyl aryl sulfides.

Whereas primary aliphatic amines generally give a mixture of secondary and tertiary amines in the Mannich reaction, primary aromatic amines can be condensed with thiophenols and formaldehyde in a 1:1:1 mole ratio to give almost exclusively moderately stable usually crystalline *N*-arylaminomethyl aryl sulfides as follows:

$$ArNH_2 + HCHO + Ar'SH \longrightarrow ArNHCH_2SAr' + H_2O$$

Under similar conditions, benzylamine, a primary aliphatic amine, condenses with *p*-chlorothiophenol and formaldehyde to give a mixture of presumably the mono- and di-(arylmercaptomethyl)amine from which *N*-benzylaminomethyl *p*-chlorophenyl sulfide is difficult to isolate.

If a mole ratio of thiophenol, primary aromatic amine, and formaldehyde of 2:1:2 is employed in this condensation, 1,3,5-triaryl-1,5-dithia-3-azapentanes are obtained:

$$ArNH_2 + 2HCHO + 2Ar'SH \longrightarrow ArN(CH_2SAr')_2 + H_2O$$

There was no evidence for the formation of a 3,4-dihydro-1,3,2H-benzo-*m*-thiazine when the condensation of the thiophenol, aniline and formaldehyde in the mole ratio of 1:1:2 was attempted. Under similar conditions phenols form the corresponding dihydrobenzo-*m*-oxazines.[4]

(1) G. F. Grillot, H. R. Felton, B. R. Garrett, H. Greenberg, R. Green, R. Clementi, and M. Moskowitz, *J. Am. Chem. Soc.*, **76**, 3969 (1954).

(2) C. M. McLeod and G. M. Robinson, *J. Chem. Soc.*, 119, 1470 (1921).

(3) F. F. Blicke, *Organic Reactions*, John Wiley & Sons, Inc., New York, N. Y., (1942), Volume 1, page 311.

(4) W. J. Burke, *et al.*, *J. Am. Chem. Soc.*, **71**, 609 (1949); **74**, 3601 (1952); **76**, 1677 (1954); **77**, 5637 (1955).

TABLE I

N-ARYLAMINOMETHYL ARYL SULFIDES, $Ar^1NHCH_2SAr^2$

Compound	Ar^1	Ar^2	M.P., °C.	Formula	Yield, %	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
I	C_6H_5	C_6H_5[a]	52–54.5	$C_{13}H_{13}NS$	56	72.52	72.66	6.09	5.89
II	C_6H_5	p-ClC_6H_4[b]	62–63.5	$C_{13}H_{12}NSCl$	16	62.51	62.64	4.84	4.58
III	p-ClC_6H_4	p-ClC_6H_4	66.2–67	$C_{13}H_{11}NSCl_2$	33	54.94	54.89	3.90	3.63
IV	o-ClC_6H_4	C_6H_5[c]	[h]	$C_{13}H_{12}NSCl$	28	62.51	62.28	4.84	4.60
V	o-ClC_6H_4	p-ClC_6H_4	64–65	$C_{13}H_{11}NSCl_2$	86	54.94	54.80	3.90	3.84
VI	m-ClC_6H_4	p-ClC_6H_4	62.5–64.5[i]	$C_{13}H_{11}NSCl_2$	23	54.94	55.04	3.90	3.46
VII	C_6H_5	2,4,6-$(CH_3)_3C_6H_2$	68–70.8	$C_{16}H_{19}NS$	19	75.06	75.19	7.44	7.46
VIII	2,4,6-$(CH_3)_3C_6H_2$	2,4,6-$(CH_3)_3C_6H_2$	157–159.2	$C_{19}H_{25}NS$	67	76.20	75.31	8.42	7.82
IX	p-$CH_3OC_6H_4$	p-ClC_6H_4	73.6–75.6	$C_{14}H_{14}NSClO$	21	60.08	60.18	5.04	5.30
X	p-$CH_3C_6H_4$	p-ClC_6H_4[d]	113–115	$C_{14}H_{14}NSCl$	[j]	63.72	64.63	5.35	4.52
XI	p-$NO_2C_6H_4$	p-ClC_6H_4[e]	139–141.5	$C_{13}H_{11}N_2O_2SCl$	74	52.97	53.18	3.76	3.18
XII	C_6H_5	C_6Cl_5[f,g]	125–135	$C_{13}H_8NSCl_5$	[k]	40.29	38.07	2.08	1.75

[a] S. Calcd.: 14.89. Found: 14.71. [b] S. Calcd.: 13.84. Found: 12.45. Cl. Calcd.: 14.20. Found: 13.72. [c] d_{26}^{26} 1.2348; n_D^{20} 1.6412. [d] A small amount of what presumably was the corresponding triarylazathiapentane was obtained. [e] Recrystallized from toluene–petroleum ether. [f] S. Calcd.: 8.28. Found: 8.09; 9.69. Cl. Calcd.: 45.75. Found: 45.28. [g] Recrystallized from toluene. [h] B.P. 120–122/1 mm. [i] B.P. 120–123/1 mm. [j] Very probably contaminated with the triarylazapentane and attempts to achieve a separation were unsuccessful. [k] A 46% yield of crude product was obtained. Although repeated recrystallization of this product from chloroform gave a product of m.p. 154–156°, analysis of this product was inferior to that of the crude product. The nature of the impurities are unknown.

In order to compare the properties of the arylaminomethyl aryl sulfides and the arylaminoethyl aryl sulfides, that is the effect of adding a second methylene group between the nitrogen and sulfur atoms, phenylaminoethyl phenyl sulfide and phenylaminoethyl *p*-chlorophenyl sulfide were prepared by the reaction of the sodium salt of the thiophenol with β-chloroethylaniline, thus:

$$ArSNa + ClCH_2CH_2NHC_6H_5 \longrightarrow ArSCH_2CH_2NHC_6H_5 + NaCl$$

EXPERIMENTAL[5]

Materials. The pentachlorothiophenol, which was kindly furnished by E. I. Du Pont de Nemours, Inc., Wilmington, Del., was recrystallized from toluene. The commercially available benzylamine was redistilled before use.

2,4,6-Trimethylbenzenesulfonyl chloride was prepared essentially by the method employed by Morgan and Cretcher in their synthesis of *p*-methoxybenzenesulfonyl chloride.[6] The former was then reduced with zinc and sulfuric acid to 2,4,6-trimethylbenzenethiol(thiomesitol) using the method of Adams and Marvel.[7]

2,4,6-Trimethylaniline (mesidine) was prepared by nitrating mesitylene[8] and reducing the nitro compound to give a yellow oil (yield 77%) boiling at 230–234°.

N-Methyl-*p*-anisidine was prepared by converting *p*-anisidine to *N*-methyl-*p*-methoxyacetanilide by the method of Hepp.[9] The latter was then converted by treatment with sodium nitrite and hydrochloric acid to *N*-nitroso-*N*-methyl-*p*-anisidine. The nitroso group was removed by the method of Reilly and Hickinbottom.[10]

β-Chloroethylaniline hydrochloride was prepared by treating β-hydroxyethylaniline (Matheson) with concentrated hydrochloric acid and thionyl chloride in the presence of chloroform according to the method of G. D. Jones.[11] A product melting at 155–160° was obtained. (Literature,[11] m.p. 155–157°.)

N-Arylaminomethyl aryl sulfides. Generally 0.1 mole of the thiophenol, 0.1 mole of the primary aromatic amine, and 0.1 mole of 35–40% formaldehyde and 20 ml. of 95% alcohol were added to the reaction flask which was then heated with stirring for 2 hr. at 80°. During this heating period the solution became cloudy and an immiscible liquid separated. The reaction mixture was then placed in the refrigerator until crystallization occurred. If crystallization did not occur on standing, the immiscible oil was extracted with ether and was then vacuum distilled. These compounds with the exception of those listed in the footnotes of Table I were purified by crystallization from ligroin. In the synthesis employing pentachlorothiophenol, benzene or toluene was used as the solvent and paraformaldehyde replaced formalin. For melting points, boiling points, yields, and analyses see Table I.

N-Methyl-N-arylaminomethyl aryl sulfides. These were prepared by the same general method as the *N*-arylaminomethyl aryl sulfides by condensing 0.1 mole of the thiophenol and 0.1 mole of the *N*-methylaniline with 0.1–0.17 mole of 35–40% formaldehyde in 20 ml. of 95% ethyl alcohol. The resulting solid products, with the exceptions noted in the footnotes of Table II, were purified by recrystallization from ligroin. Like the *N*-arylaminomethyl aryl sulfides, these compounds would form neither picrates nor *p*-nitrobenzoates. For data concerning these compounds see Table II.

1,3,5-Triaryl-1,5-dithia-3-azapentanes. In the reaction flask were placed 0.1 mole of the thiophenol, 0.05 mole of aniline, 0.1 mole of 35–40% formaldehyde, and 20 ml. of 95% alcohol. Upon heating for 2 hr. at 80° with stirring, immiscible oils separated that crystallized upon cooling and standing. The resulting solids were recrystallized from ligroin. Data for these compounds appear in Table III.

(5) Carbon, hydrogen, and nitrogen analyses were performed by Drs. Weiler and Strauss, Oxford, England, and Mr. Richard Downing of Bristol Labs., Inc., Syracuse, N. Y. The sulfur and chlorine analyses were performed by R. E. S.

(6) M. S. Morgan and L. H. Cretcher, *J. Am. Chem. Soc.*, **70**, 375 (1948).

(7) R. Adams and C. S. Marvel, *Org. Syntheses*, **Coll. Vol. 1**, Second Edition, p. 504.

(8) G. Powell and F. R. Johnson, *Org. Syntheses*, **14**, 68 (1934).

(9) P. Hepp, *Ber.*, **10**, 327 (1877).

(10) J. Reilly and W. J. Hickinbottom, *J. Chem. Soc.*, **115**, 180 (1919).

(11) G. D. Jones *et al.*, *J. Org. Chem.*, **9**, 125 (1944).

TABLE II

N-ARYL-*N*-METHYLAMINOMETHYL ARYL SULFIDES, $Ar^1N(CH_3)CH_2SAr^2$

Compound	Ar^1	Ar^2	M.P., °C.	Formula	Yield, %	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
XIII	C_6H_5	C_6H_5[a]	36.4–38	$C_{14}H_{15}NS$	71	73.32	73.70	6.59	6.59
XIV	C_6H_5	*p*-ClC_6H_4	44.6–46.7	$C_{14}H_{14}NSCl$	72	63.72	64.36	5.35	5.34
XV	C_6H_5	2,4,6-$(CH_3)_3C_6H_2$[b]	51.8–52.8	$C_{17}H_{21}NS$	89	75.60	75.32	7.80	8.01
XVI	C_6H_5	C_6Cl_5[c]	118–121.4	$C_{14}H_{10}NSCl_5$	91	41.87	42.09	2.51	2.50
XVII	*p*-$NO_2C_6H_4$	*p*-ClC_6H_4[d]	91.8–93.6	$C_{14}H_{13}N_2O_2SCl$	66	54.45	54.56	4.24	4.28
XVIII	*p*-$CH_3OC_6H_4$	*p*-ClC_6H_4	56.6–58.2	$C_{15}H_{16}NOSCl$	93	61.26	61.61	5.49	5.61

[a] S. Calcd.: 13.98. Found: 13.98. [b] Recrystallized from alcohol. [c] Recrystallized from toluene. [d] Recrystallized from toluene-petroleum ether.

TABLE III

1,3,5-TRIARYL-1,5-DITHIA-3-AZAPENTANES, $Ar^1SCH_2NCH_2SAr^1$ (with Ar^2 on N)

Compound	Ar^1	Ar^2	M.P., °C.	Formula	Yield, %	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
XIX	C_6H_5	C_6H_5	50.2–52.2	$C_{20}H_{19}NS_2$	56	71.18	71.58	5.68	5.69
XX	*p*-ClC_6H_4	C_6H_5	60.6–61.4	$C_{20}H_{17}NS_2Cl_2$	74	59.11	59.31	4.22	4.08
XXI	*p*-ClC_6H_4	*p*-$CH_3C_6H_4$	71–74	$C_{21}H_{19}NS_2Cl$	[a]	60.01	61.02	4.56	4.81

[a] Obtained as a by-product in the preparation of the corresponding arylaminomethyl aryl sulfide and is probably contaminated with the latter compound.

N-Benzylaminomethyl p-chlorophenyl sulfide (*Compound* XXII). This compound was prepared in the same general manner as the *N*-arylaminomethyl aryl sulfides by condensing 0.1 mole of benzylamine, 0.1 mole of *p*-chlorobenzenethiol and 0.1 mole of 35–40% formaldehyde in 20 ml. of 95% alcohol. A white solid formed when the thiol and amine were mixed, but this dissolved upon the addition of the alcohol. When the formaldehyde solution was added, an immiscible liquid formed which soon crystallized. Eight grams (30% yield) of fine white needles, m.p. 54–55.6° was obtained. This, however, appeared to be a mixture as it formed a picrate that melted in the range 81–145°. A small quantity of material as fine needles was obtained from the alcoholic mother liquor. This substance melted at 71–73° and the following analyses indicated that it was the substance sought.

Anal. Calcd. for $C_{14}H_{14}NSCl$: C, 63.72; H, 5.35; neut. equiv., 264. Found: C, 64.11; H, 4.63; neut. equiv., 263.

N-Phenylaminoethyl p-chlorophenyl sulfide (*Compound* XXIII). In a beaker was placed 10 g. (0.06 mole) of β-chloroethylaniline hydrochloride and sufficient water to bring the solid into solution. To this was added 4.1 g. (0.03 mole) of anhydrous potassium carbonate, whereupon a dark colored oil separated. This solution was extracted with ether and the extracts were dried over anhydrous magnesium sulfate.

In a 500 ml. round bottom flask fitted with a mercury sealed stirrer, dropping funnel, condenser, and drying tube filled with calcium chloride were placed 100 ml. of absolute alcohol and 3 g. (0.13 mole) of sodium. When the sodium had dissolved, 0.06 mole of *p*-chlorothiophenol in 20 ml. of absolute alcohol was added. Then the filtered ethereal solution of β-chloroethylaniline, equivalent to 7.9 g. (0.06 mole) of the free base was slowly added and the resulting reaction mixture was refluxed for 2 hr.

After cooling, the precipitated sodium chloride was removed by filtration and the alcohol and ether were evaporated under reduced pressure. The solid residue that remained was dissolved in ether and this solution was then extracted with 200 ml. of 10% hydrochloric acid. The white solid that floated between the ether and water layer was collected on a filter and was washed with ether. It was then placed in a beaker and water was added to make a slurry. Sodium hydroxide (10%) was added until the solution was distinctly alkaline. Ether extraction of this solution followed.

Meanwhile 10% sodium hydroxide was added to the acid wash water. The white solid that separated was extracted with ether and this extract was combined with the other ether extracts. After drying the combined ether extracts over anhydrous magnesium sulfate, the ether was removed under reduced pressure. The resulting residue was dissolved in methanol and cooled, whereupon an amorphous pink powder formed. Most of the color was removed by recrystallizing from methanol using Nuchar. A second recrystallization employed petroleum ether as the solvent. Melting point 45.2–46.6°. Yield 38%.

Anal. Calcd. for $C_{14}H_{14}NSCl$: C, 63.72; H, 5.35. Found: C, 63.18; H, 5.16.

Picrate. Melting point 126.8–127.6°.

Anal. Calcd. for $C_{20}H_{17}N_4O_7SCl$: N, 11.37. Found: N, 11.35.

N-Phenylaminoethyl phenyl sulfide (*Compound* XXIV). This compound was prepared in the same manner as the corresponding *p*-chlorophenyl compound described above, employing thiophenol in place of the *p*-chlorothiophenol. Following the neutralization of the hydrochloric acid extract with 10% sodium hydroxide, a yellow oil was obtained. This oil was dissolved in ether and the resulting solution was dried over anhydrous magnesium sulfate. Upon removal of the ether, 12.1 g. of an oil remained.

After removal under reduced pressure of a few drops of low boiling material, this liquid was dissolved in acetone. Nuchar removed part of the color and water was added, causing an oily liquid to separate. Removal of the water and acetone by evaporation produced a violet color residue that was then recrystallized from ligroin. It was then recrystallized from alcohol using Nuchar as a decolorizing agent. This was followed by a recrystallization from ligroin. Melting point 35–41°. Yield 21%.

Anal. Calcd. for $C_{14}H_{15}NS$: C, 73.32; N, 6.59. Found: C, 73.29; H, 6.56.

Infrared Spectra. Infrared spectrograms of compounds I, II, V, VII, VIII, XII, XIII, XIV, XV, XVI, and XIX were prepared by Samuel P. Sadtler and Sons, Inc., 1517 Vine St., Philadelphia, Pa.

The following observations have been made from the infrared spectra:

1. In support of the sulfide structure assigned to these compounds, the absorption peak in the 3.7–3.9 micron region, characteristic of the SH group[12] is absent in these spectra.

2. In the *N*-arylaminomethyl aryl sulfides a sharp spike occurs at 2.9 microns characteristic of the NH stretching in secondary amines.[13]

3. An absorption band in the 8-micron region characteristic of aromatic amines[13] is found in the spectra of all the *N*-arylaminomethyl aryl sulfides.

4. An absorption band in the range of 7.4–7.6 microns and another (a triplet) in the 8.1–8.5 micron region, characteristic of tertiary amines[13] are present in the spectra of the *N*-methyl-*N*-arylaminomethyl aryl sulfides.

5. A new absorption band characteristic of these latter tertiary amines is found as a "triplet" with a sharp absorption in the 10-micron region. The ortho substituted secondary amines, having a "triplet" in the 8-micron region, may be differentiated by the lack of this triplet in the 10-micron region.

6. The infrared spectra of 2,4,6-trimethylphenylaminomethyl 2,4,6-trimethylphenyl sulfide (compound VIII) indicates a definite existence of steric hindrance which must be due to the interaction of the many methyl groups attached to the ortho positions in the aromatic nuclei.

Potentiometric titrations and the basicities of the arylaminomethyl and ethyl aryl sulfides. Of the *N*-arylaminomethyl aryl sulfides, compounds I, II, VII, and XII, when titrated with perchloric acid in glacial acetic acid, gave end points at acid volumes that represent neutral equivalents that are approximately double the formula weight. This was true whether an indicator was used to determine the end point or when a potentiometric titration was performed.

When the neutral equivalent of compound II was determined by a conductiometric titration, using the same perchloric acid in acetic acid and when this compound was titrated potentiometrically with a solution of acetylium perchlorate, $CH_3CO^+ClO_4^-$, in acetic acid, the neutral equivalent was equal to the formula weight.

The failure of the true equivalence point to appear in a potentiometric titration may be analogous to the failure to detect the third equivalence point in the titration of H_3PO_4 *vs.* NaOH, the fact that the acidity of $HPO_4^=$ is close to that of water and the acidity of $Ar—S—CH_2—\overset{+}{N}H_2—Ph$ may be close to acetic acid (Leveling Effect).

Placing a methoxyl or methyl group para or methyl groups in the 2, 4, and 6 positions to the amine in the *N*-arylaminomethyl aryl sulfides apparently increases the basicity of these compounds. These groups are known to be nucleophilic and this property seems to make up the deficit of electrons on the amine group. The NE/FW is no longer equal to two but is shifted toward a value of one, indicating that electrons are becoming more available at the site of the amine nitrogen atom.

It was noted that when a chlorine atom is located ortho, meta, or para to the amine group in these compounds, the condensation product is neutral towards $HClO_4$ in glacial acetic acid. A para nitro group, another electrophilic group, as expected also produces a neutral compound. Chlorine, when attached to an aromatic nucleus is not only ortho-para directing but also deactivates the ring. It is felt that the *N*-(chlorophenyl)aminomethyl aryl sulfides are examples of the dominance of the inductive effect of the halogens over the mesomeric effect.

It is now felt that steric effects, the existence of which is supported by infrared evidence, play an important role in the case of the compound prepared from thiomesitol and mesidine. Here the NE/FW was approximately 1.5 (in the case of the *p*-CH_3 and *p*-CH_3O compound the value was 1.2). The ortho methyl groups on the amine and thiol nucleus make it more difficult for the protonating agent to attack the nitrogen atom.

One may presume that when the sulfide linkage is on an alpha carbon of an alkyl group in an arylaminoalkyl aryl sulfide, the combined electron withdrawal of the sulfur atom and the aromatic nucleus so reduce the availability of the electrons on the nitrogen atom that the typical aromatic amine properties of moderate basicity and ready salt formation are partially destroyed. Note that these compounds do not form stable picrates.

Replacing the aromatic amine with diethylamine, piperidine, or morpholine removes one of the electron withdrawing groups, the aromatic ring. The electron withdrawal of the sulfur atom must be much less than the aromatic ring, for compounds of these latter types give neutral equivalents equal to the formula weights and usually form stable picrates.[1]

Except for the sulfide obtained from *N*-methyl-*p*-nitroaniline, the presence of a methyl group on the nitrogen atom in addition to the phenyl group as in *N*-methyl-*N*-phenylaminomethyl phenyl sulfide increases the electron density on the nitrogen atom sufficiently to permit a NE/FW equal to unity, but not sufficient to form stable salts. However, further proof of the powerful electrophilic character of the nitro group is found when this group is placed para to the amine group in these *N*-methyl compounds. The resulting compound is neutral in the $HClO_4$/HAc titration.

The 1,3,5-triaryl-1,5-dithia-3-azapentanes were neutral when titrated with perchloric acid in glacial acetic acid. Thus the electron withdrawal of the two thiomethyl and an aryl group reduces the basicity of the nitrogen atom so that the resulting tertiary amine is neutral.

If the sulfur and nitrogen atoms are separated by two methylene groups, as in the arylaminoethyl aryl sulfides, neutral equivalents equal to the formula weight are obtained. The arylaminoethyl aryl sulfides also form stable picrates. This "insulating effect" is a well documented phenomenon.[14]

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(12) F. Bell, *Ber.*, 61, 1918 (1928).

(13) F. A. Miller, *Organic Chemistry, An Advanced Treatise*, H. Gilman, Ed., John Wiley & Sons, Inc., New York, 1953, Vol. III, p. 140.

(14) E. R. Alexander, *Principles of Ionic Organic Reactions*, John Wiley and Sons, Inc., New York, 1950, p. 8.

[CONTRIBUTION FROM AVERY LABORATORY, THE UNIVERSITY OF NEBRASKA]

Utility of the Methanesulfonyl Blocking Group. II.[1] Synthesis of Isovanillic Acid and Methanesulfonyl Derivatives of Phenolic Acids[2]

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Received November 17, 1958

A procedure for synthesis of isovanillic acid *via* oxidation of mesyl isovanillin is presented. Mesyl[3] derivatives of vanillic, isovanillic, and protocatechuic acids are described. Mesylation of these phenolic acids in pyridine leads to complex products, infrared spectra of which reveal presence of the carboxylic ester function.

The methanesulfonyl blocking group was introduced in 1937 by Helferich and Hiltmann,[4,5] whose initial studies were concentrated in the sugar area. Subsequently, this block was extended to phenolic compounds,[6] including the phenolic aldehyde vanillin,[7] and to amino acids.[8] Helferich and Papalambrous[6] pointed out the acid stable, base labile character of the mesyloxy group in mesyl derivatives of phenolic compounds.

In recent years, studies in this laboratory have demonstrated the remarkable stability of the mesyloxy group under conditions simultaneously strongly acidic and strongly oxidizing,[1] and the utility of the mesyl block in synthesis of mesyloxy acids from *p*-tolyl methanesulfonate[1] and from mesyl blocked phenolic aldehydes.[9,10] It has been demonstrated further that mesyl blocked phenolic acids cannot be prepared by direct mesylation of phenolic acids because of predominant formation of complex products containing polyesters.[11] The present paper describes a synthetic procedure for isovanillic acid based on oxidation of mesyl isovanillin under acidic conditions, preparation of mesyl vanillic acid and dimesyl protocatechuic acid by oxidation of the appropriate mesylated aldehyde, and the formation of complex, ester-type products from mesylation of vanillic, isovanillic, and protocatechuic acids.

The phenolic aldehydes were esterified with methanesulfonyl chloride in pyridine. Mesyl isovanillin was readily prepared and purified. However, dimesyl protocatechualdehyde was obtained in satisfactory yield only under short term mesylation. When a longer reaction period was used, the product was highly colored and difficult to purify.

Oxidation of all mesyl phenolic aldehydes was carried out in acidic dichromate solution. Crude mesyl isovanillin was satisfactory for oxidation. The oxidation product, mesyl isovanillic acid, was isolated and characterized. However, for synthesis of isovanillic acid, isolation of mesyl isovanillic acid was not necessary. The relatively slight solubility of unreacted mesyl isovanillin (in the crude reaction product) in dilute base permitted its ready removal by filtration. Hydrolysis of mesyl isovanillic acid in the alkaline filtrate gave isovanillic acid in 91% yield (corrected for recovered mesyl isovanillin). A 73% quantity of mesyl isovanillin was converted to the acid, and the recovered aldehyde was sufficiently pure for reoxidation without additional purification. Application of this general oxidation procedure to the known mesyl vanillin[7] gave mesyl vanillic acid. In the oxidation of dimesyl protocatechualdehyde, a rather large excess of oxidizing agent was used. Even so, there was an apparent recovery of a considerable quantity of the mesyl aldehyde.

On the basis of earlier studies in this laboratory,[11] mesylation of a phenolic acid in pyridine would not be expected to give the mesyl phenolic acid. Mesylation of the phenolic acids in the present work gave bicarbonate insoluble products, the infrared spectra of which (Table I) indicate the presence of the carboxylic ester function. Spectral data for the authentic mesyl phenolic acids are included in Table I for comparison.

The spectral data of the present study, combined with the data of the previous work,[11] indicate that mesylation products of phenolic acids fall into two classes:

Class I: Mesylation products containing both the carboxylic acid and ester function. The fol-

(1) Part I: J. H. Looker and D. N. Thatcher, *J. Org. Chem.*, **19**, 784 (1954).

(2) This investigation was supported by a research grant (E-1703) from the National Institute of Allergic and Infectious Diseases, Public Health Service.

(3) Mesyl = methanesulfonyl; for a more thorough discussion of nomenclature, see R. S. Tipson, *Adv. in Carbohydrate Chem.*, **8**, 108 (1953).

(4) B. H. Helferich and R. Hiltmann, *Ann.*, **531**, 160 (1937).

(5) Aryl methanesulfonates were described many years ago by C. Schall, *J. prakt. Chem.*, **48**, 241 (1893). However, the preparative procedure employed did not involve a direct introduction of the mesyl block by use of methanesulfonyl chloride.

(6) B. Helferich and P. Papalambrous, *Ann.*, **551**, 235 (1942).

(7) B. Helferich and P. Papalambrous, *Ann.*, **551**, 245 (1942).

(8) B. Helferich and H. Grünert, *Ann.*, **545**, 178 (1940).

(9) J. H. Looker and C. H. Hayes, *J. Am. Chem. Soc.*, **79**, 745 (1957).

(10) For a very recent, interesting example of the applicability of the mesyl block to syntheses of *m*-hydroxyphenyl methyl sulfoxide, see F. G. Bordwell and P. J. Boutan, *J. Am. Chem. Soc.*, **79**, 717 (1957).

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TABLE I

INFRARED SPECTRAL DATA[a,b] FOR PHENOLIC ACID MESYL DERIVATIVES AND MESYLATION PRODUCTS

Compound	M.P. or Range, °C.	Infrared Maxima, cm.$^{-1}$		
		Acid[c] CO	Acid[c] OH	Ester[c] CO
Mesyl derivative of:				
Vanillic acid	167–169	1687	2680, 2650	—
Isovanillic acid	226–227	1685 (1672?)	2650, 2608	—
Protocatechuic acid	208–210	1693	2710, 2650	—
Mesylation product of:				
Vanillic acid	155–177 (dec.)	1692	2650	1733
Isovanillic acid	125–151	1690, 1685	2610	1732
Protocatechuic acid	120–165	—	—	1750

[a] Spectra of Nujol mulls were determined with a Perkin-Elmer Model 21 recording spectrophotometer. [b] All bands are medium or strong, except OH bands. [c] Band-structure correlations are in accordance with L. J. Bellamy, *The Infra-red Spectra of Complex Molecules*, John Wiley and Sons, Inc., New York, N. Y., 1954, pp. 5–9.

lowing acids give this type of product: *m*- and *p*-hydroxybenzoic, 3,5-diiodo-4-hydroxybenzoic, vanillic, and isovanillic acids.

Class II: Mesylation products containing the carboxylic ester function, but not the carboxylic acid group. Salicylic, gallic, and protocatechuic acids give this type of mesylation product.

Class I mesylation products very probably are closely related to depsides in structure.[11] Class II mesylation products, while of less certain constitution, may contain cyclic structures or cross-linked polymers. As previously demonstrated,[11] the mesylation product of salicylic acid contains the cyclic ester, trisalicylide.

EXPERIMENTAL[12]

Mesyl isovanillin (3-methanesulfonyloxy-4-methoxybenzaldehyde). A 150 g. quantity of isovanillin was dissolved in 600 ml. of reagent grade pyridine and cooled in ice. To this solution was added 90 ml. of methanesulfonyl chloride. The reaction mixture stood in an ice bath 4 hr., then at room temperature overnight. The mixture then was poured into 2 l. of ice water to which 600 ml. of concentrated hydrochloric acid previously had been added. The precipitated crude product was collected by filtration, washed with cold water, and air-dried; yield, 218 g. (96%), m.p. 80–89°. This product could be recrystallized with 85% efficiency from dilute methanol to give the aldehyde, m.p. 86–89°. Additional crystallization from dilute methanol and methanol gave analytically pure, colorless mesyl isovanillin, m.p. 87–89°.

Anal. Calcd. for $C_9H_{10}O_5S$: C, 46.87; H, 4.38; S, 13.84. Found: C, 47.00; H, 4.57; S, 14.00.

Dimesyl protocatechualdehyde[3,4-bis(methanesulfonyloxy)-benzaldehyde]. A 2.00 g. quantity of protocatechualdehyde (buff-colored, m.p. 150–154°) was dissolved in 20 ml. of reagent grade pyridine. The resulting mixture was cooled in ice to 0–5°, and a 4.4 ml. quantity of methanesulfonyl chloride was added. The reaction mixture stood in an ice bath for 2 hr. A 0.6 ml. quantity of water was added cautiously to the cold solution, and the resulting mixture permitted to stand in an ice bath for 10 min. The reaction mixture then was poured into 200 ml. of cold water containing 20 ml. concentrated hydrochloric acid. The crude cream-colored product precipitated immediately, and was collected by filtration, washed with water, air-dried 24 hr., and then dried *in vacuo* over phosphorus pentoxide and concentrated sulfuric acid for 48 hr.; yield, 3.82 g. (89.7%), m.p. 110–114.5°. This material was of purity suitable for oxidation. Recrystallization of the total crude from 20–22 ml. of chloroform led to a 74.7% recovery of virtually colorless product, m.p. 110–114°. Crystallization also was possible from acetone or dilute methanol.

Analytically pure material was obtained by dissolving a fraction of crude aldehyde, m.p. *ca.* 110–1125°, (possibly contaminated with dimesyl protocatechuic acid formed by air oxidation) in ethyl acetate, extracting with two 50-ml. portions of sodium bicarbonate, back extracting the latter with ethyl acetate, and combining the ethyl acetate extracts. The latter were washed with water and dried over anhydrous sodium sulfate. Solvent removal at room temperature *in vacuo* gave a crystalline residue, m.p. 110–115°. The residue was washed with 2*N* sodium hydroxide, then with water, and dried in a vacuum desiccator over phosphorus pentoxide. A final crystallization from chloroform, with cooling of the chloroform solution in ice, gave analytically pure, colorless, dimesyl protocatechualdehyde, m.p. 112.5–114.5°.

Anal. Calcd. for $C_9H_{10}O_7S_2$: C, 36.73; H, 3.42; S, 21.79. Found: C, 36.55; H, 3.39; S, 21.57.

Mesyl vanillic acid (3-methoxy-4-methanesulfonyloxybenzoic acid). A 34.5 g. quantity of crude mesyl vanillin[7] (prepared from vanillin and methanesulfonyl chloride in pyridine) was suspended in a solution prepared by dissolving 15.0 g. of potassium dichromate in a sulfuric acid solution (prepared from 48 ml. concentrated sulfuric acid added to 198 ml. of water). Upon heating the reaction mixture to 65° with constant stirring, an exothermic reaction commenced. The reaction vessel was removed from the heat source as the temperature rose to 78°. After the initial heat of reaction subsided, the heterogeneous mixture was heated as necessary to maintain the temperature between 70–75° for 45 min. The reaction mixture was cooled in ice, diluted with 150 ml. of water, and again cooled in ice. The crude product was collected by filtration, washed with water, and air-dried; yield 37 g., melting 95–140°. The total crude product was washed with 2 l. of 5% sodium bicarbonate. The extract upon acidification gave 6.3 g. of mesyl vanillic acid, m.p. 164–168°. Recrystallization from dilute ethanol and then from ethyl acetate gave the analytically pure, colorless acid, m.p. 167–169°.

Anal. Calcd. for $C_9H_{10}O_6S$: C, 43.90; H, 4.09; S, 13.02. Found: C, 44.03; H, 4.23; S, 13.04.

Mesyl isovanillic acid (3-methanesulfonyloxy-4-methoxybenzoic acid). An 11.5 g. quantity of mesyl isovanillin, m.p. 86–89°, was suspended in a solution prepared by dissolving 5.0 g. of potassium dichromate in 78 ml. of 30% sulfuric acid. The resulting heterogeneous mixture was heated with constant stirring at 60–70° for 1 hr. After the reaction mixture had cooled to room temperature, the crude product was collected by filtration and washed free of chromium salts with

(12) Melting points are uncorrected. Analyses are by Micro-Tech Laboratories, Skokie, Ill.

water. Exhaustive extraction with 5% sodium bicarbonate gave 2.2 g. of unreacted mesyl isovanillin, m.p. 84–88°, which was removed by filtration. Acidification of the bicarbonate filtrate with concentrated hydrochloric acid gave 8.0 g. of mesyl isovanillic acid, m.p. 217–226°. Analytically pure acid, m.p. 226–227°, was obtained by crystallization from 300 ml. of boiling ethyl acetate, and then two additional recrystallizations from the same solvent. Recrystallization also was possible from 95% ethanol, in which the acid was appreciably more soluble.

Anal. Calcd. for $C_9H_{10}O_6S$: C, 43.90; H, 4.09; S, 13.02. Found: C, 44.08; H, 4.13; S, 12.88.

Isovanillic acid. A dichromate solution was prepared by dissolving 47.0 g. of potassium dichromate in a sulfuric acid solution (prepared by adding 150 ml. of concentrated sulfuric acid to 620 ml. of water). This dichromate solution first was heated to 60°, and then a 107.5 g. quantity of crude mesyl isovanillin, m.p. 85–89°, was added. Upon heating the reaction mixture to 71° with constant stirring, an exothermic reaction started. The mixture was removed from the heat source until the exothermic reaction subsided (*ca.* 20 min.), and then was heated intermittently to maintain temperature at 72–75° for 40 min. The temperature was increased over a 30-minute period to 90°. The reaction mixture was permitted to cool, and stood at room temperature overnight. The crude product was collected by filtration, washed free of chromium salts on the filter, and then with an additional 1 liter quantity of water; yield, after air drying, 110 g., m.p. 210–218°, with softening at 185°. The total crude product was dissolved as much as possible in approximately 2*N* sodium hydroxide (prepared by dissolving 107 g. of sodium hydroxide in 1330 ml. of water). Unreacted mesyl isovanillin (21.5 g., m.p. 84–88°) was removed by filtration, and retained for subsequent reoxidation. The alkaline filtrate after standing at room temperature for 24 hr. was acidified with concentrated hydrochloric acid. The precipitated acid was collected by filtration, washed well with water, and air-dried for several weeks; yield, 57.5 g. (91%, based on 86 g. of mesyl isovanillin), m.p. 244–249°. Recrystallization was effected by heating the total acid with 1400 ml. of absolute ethanol under reflux for 90 min., filtering, and permitting the filtrate to cool for 2.5 hr., or until the temperature was *ca.* 35°. The crystalline isovanillic acid was collected by filtration of the warm mixture, and air-dried overnight; yield, 32.8 g., m.p. 247–249.5° (lit. m.p.[13] 251°). Additional isovanillic acid was recovered by concentration of the mother liquor. A higher efficiency of crystallization (66%) was realized by permitting crystallization mixtures to cool to room temperature before filtration. However, the acid thus obtained was rather highly colored.

Acetylation of isovanillic acid, m.p. 247–249.5°, by the procedure of Lesser and Gad,[14,15] gave *O*-acetylisovanillic acid, m.p. 211.0–212.5° (lit. m.p.[15] 212–215°).

Dimesyl protocatechuic acid [3,4-bis(methanesulfonyloxy)-benzoic acid]. A 1.47 g. quantity of dimesyl protocatechualdehyde was suspended in a dichromate solution, prepared by dissolving 0.75 g. of potassium dichromate in 12 ml. of 30% sulfuric acid. The reaction mixture was heated at 70–75° for 90 min. under constant stirring, and then the temperature gradually was increased to 95°. The mixture was cooled, permitted to stand at room temperature overnight, and diluted to a volume of 25 ml. The crude product was collected by filtration, washed free of chromium salts on the filter, and air-dried for several days; yield, 1.45 g., m.p. 188–195°, with sintering at 170°. The crude acid was washed with three successive 50-ml. portions of 5% sodium bicarbonate. Bicarbonate insoluble material (Fraction A, 0.73 g., melting 170–187°) was collected by filtration and retained. Acidification of the bicarbonate extracts gave 0.47 g. of crude dimesyl protocatechuic acid, m.p. 195–201°. Additional acid was obtained by extracting an ethyl acetate solution of Fraction A with 5% sodium bicarbonate; acidification gave 0.28 g., m.p. 206–210°. Total yield of colorless dimesyl protocatechuic acid thus was 0.75 g. Analytically pure acid was obtained by recrystallizing total acid thrice from 95% ethanol, and the crystals, after being dried *in vacuo* 6 hr. over boiling water, melted at 208–210°.

Anal. Calcd. for $C_9H_{10}O_8S_2$: C, 34.84; H, 3.25; S, 20.66. Found: C, 35.08; H, 3.39; S, 20.95.

Mesylation of vanillic and isovanillic acids. A 1.36-g. quantity of the acid was dissolved in 7.5 ml. of reagent grade pyridine, cooled to 5°, mixed with 0.7 ml. of methanesulfonyl chloride and allowed to stand for 20 hr. Product isolation as previously described,[11] followed by washing with 50 ml. boiling water and 50 ml. 5% sodium bicarbonate (insoluble material retained), gave 0.88 and 0.78 g. of the mesylation products of vanillic and isovanillic acids, respectively. Products were dried in a vacuum desiccator over phosphorus pentoxide prior to infrared analysis.

Mesylation of protocatechuic acid. A 3.08-g. quantity of protocatechuic acid was dissolved in 30 ml. of reagent pyridine, cooled to 5°, mixed with 3.4 ml. of methanesulfonyl chloride and allowed to stand for 23 hr. Product isolation as previously described,[11] followed by washing with 100 ml. of 5% sodium bicarbonate and then with several hundred ml. of water at room temperature (insoluble material retained), gave 1.58 g. of the mesylation product. The latter was dried in a vacuum desiccator over phosphorus pentoxide before infrared spectral analysis.

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(13) E. Späth and G. Burger, *Ber.*, **59**, 1494 (1926).

(14) R. Lesser and G. Gad, *Ber.*, **59B**, 233 (1926).

(15) The specific procedure employed was that of V. Deulofeu and N. Schopflocher, *Gazz. chim. ital.*, **83**, 449 (1953).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MICHIGAN STATE UNIVERSITY]

Tetra- and Pentacyclic Benzimidazole Compounds as Analogs of Some Indole Alkaloids

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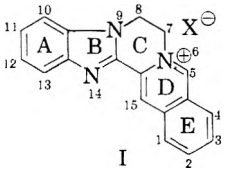
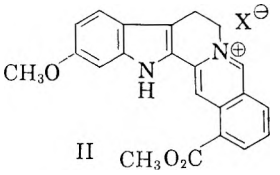
Received January 6, 1959

The preparation of the tetracyclic quaternary salt, 6,7-dihydrobenzimidazo[1,2-*a*]pyrido[2,1-*c*]pyrazinium bromide and its reduced form, 1,2,3,4,6,7-hexahydro-13*bH*-benzimidazo[1,2-*a*]pyrido[2,1-*c*]pyrazine is described. The synthesis of the corresponding pentacyclic quaternary salt, 7,8-dihydrobenzimidazo[1,2-*a*]isoquino[3,2-*c*]pyrazinium bromide and the form in which the D ring is reduced, 5,6,7,8-tetrahydro-14*bH*-benzimidazo[1,2-*a*]isoquino[3,2-*c*]pyrazine, is also described. The ultraviolet absorption curves are discussed.

Recent interest in benzimidazole analogs of physiologically active indole compounds, which has included the analogs of tryptophan[2] and serotonin[3,4] prompted us to report the synthesis of the benzimidazole analog (I) of the basic ring system of alstoniline[5,6] (II) as well as the corresponding tetracyclic quaternary salt (IV). It was hoped that such compounds or their reduced forms would possess hypotensive activity.



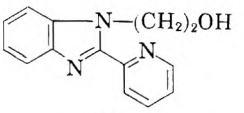
I



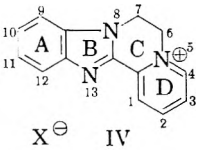
II

Attempts to benzoylate 2-phenylbenzimidazole have not been successful.[7] Furthermore, in our hands 2 - (2′ - pyridyl)benzimidazole[8] and 2 - (3′ - isoquinolyl)benzimidazole failed to alkylate in the 1 position with various active halides. In view of these findings it appeared necessary to introduce the substituent on the nitrogen of the 1 position prior to cyclization and introduction of an aryl group in the 2 position of the benzimidazole structure.

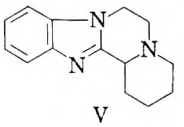
This approach was best achieved by treatment of *o*-nitrobromobenzene with ethanolamine forming *o*-nitro-*N*-(2-hydroxyethyl)aniline. Reduction of the nitro group provided *o*-amino-*N*-(2-hydroxyethyl)aniline which, in turn, was condensed with pyridine-2-carboxaldehyde in the presence of nitrobenzene to yield 1-(2′-hydroxyethyl)-2-(2′-pyridyl)benzimidazole (III). Treatment of III with refluxing hydrobromic acid effected ring closure to the quaternary salt, 6,7-dihydrobenzimidazo-[1,2-a]pyrido[2,1-*c*]pyrazinium bromide (IV). Reduction of the D ring of IV using hydrogen and platinum oxide gave the corresponding 1,2,3,4,6,7-hexahydro-13*bH*-benzimidazo[1,2-*a*]pyrido[2,1-*c*]-pyrazine (V).



III

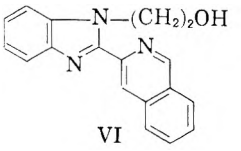


IV

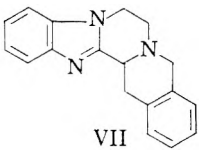


V

Isoquinoline-3-carboxaldehyde was similarly condensed with *o*-amino-*N*-(2-hydroxyethyl)aniline and gave 1-(2′-hydroxyethyl)-2-(3′-isoquinolyl)benzimidazole (VI). Also isolated from this reaction was a second product, a yellow solid melting at 246.5–247°. The identity of this material has not been established.



VI



VII

Treatment of VI with refluxing 48% hydrobromic acid effected ring closure to form 7,8-dihydrobenzimidazo[1,2-*a*]isoquino[3,2-*c*]pyrazium bromide (I). Reduction of the D ring using hydrogen and platinum oxide provided the 5,6,7,8-tetrahydro-14*bH* - benzimidazo[1,2 - *a*]isoquino[3,2 - *c*]pyrazine (VII).

Ultraviolet absorption spectra. Because of the interest in these compounds the ultraviolet absorption spectra of the 2-(2′-pyridyl)- and 2-(3′-isoquinolyl)benzimidazoles as well as the tetra- and pentacyclic quaternary salts and their reduced forms were examined.

The spectra of the benzimidazoles with a 2-pyridyl and 3-isoquinolyl group substituted in the

(1) Present address: Chas. Pfizer and Co., Inc., Brooklyn, N. Y.

(2) P. Mamlis, V. Petrow, and B. Sturgeon, *J. Chem. Soc.*, 1600 (1950).

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(4) W. B. Wheatley and G. F. Stiner, *J. Org. Chem.*, 22, 923 (1957).

(5) R. C. Elderfield, and S. L. Wythe, *J. Org. Chem.*, 19, 683 (1954).

(6) R. C. Elderfield and O. L. McCurdy, *J. Org. Chem.*, 21, 295 (1956).

(7) H. Hübner, *Ann.*, 208, 307 (1881).

(8) D. Jerchel, H. Fischer, and M. Kracht, *Ann.*, 575, 162 (1952).

2 position of the benzimidazole were determined in ethanol and in 0.01*N* hydrochloric acid. The use of 0.01*N* hydrochloric acid as a solvent caused a broadening or smearing out in solution of the absorption peaks as well as a hyposochromic shift of the maxima and minima. 2-(3′-Isoquinolyl)benzimidazole shows some absorption above 340 mμ.

The spectra of the tetra- and pentacyclic quaternary salts, IV and I, in water, show absorption in the same general region as those of the pyridyl- and isoquinolyl- benzimidazoles in addition to absorption above 340 mμ. This absorption at longer wave lengths was anticipated because of the yellow color of the quaternary salts.

Reduction of the D ring of IV resulted in a compound (V) whose spectrum differed markedly from those thus far mentioned and was almost identical with those of 2-dialkylaminomethylbenzimidazoles.[3] The maxima and minima of the benzimidazole spectra are recorded in Table I.

TABLE I

ABSORPTION SPECTRA CHARACTERISTICS OF SOME BENZIMIDAZOLES

(Wave length in mμ)

Benzimidazole	Maxima	Minima	Shoulder
2-(2′-Pyridyl)[a]	240	237	245
	310	255	320
2-(3′-Isoquinolyl)[a]	235	265	
	280	288	
	322	334	
	339		
6,7-Dihydrobenzimidazo-[1,2-*a*]pyrido[2,1-*c*]-pyrazinium bromide[b]	245	233	
		265	
7,8-Dihydrobenzimidazo-[1,2-*a*]isoquino[3,2-*c*]-pyrazinium bromide[b]	247	261	286
	281	300	
	337		
1,2,3,4,6,7-Hexahydro-13*bH*-benzimidazo[1,2-*a*]-pyrido[2,1-*c*]pyrazine[a]	254	228	
	275	264	
	282	279	
2-Dialkylaminomethyl[c]	245	226	248
	277	260	
	283	278	

[a] In 95% ethanol. [b] In water. [c] Ref. 9.

EXPERIMENTAL[10,11]

Preparation of benzimidazoles. o-Nitro-N-(2-hydroxyethyl)-aniline. To 190 ml. of ethanolamine containing 27.5 g. (0.24 mole) of *o*-nitrobromobenzene was added 4.5 g. of anhydrous cupric chloride. The resulting mixture was heated on a steam bath for 90 min., care being taken that the temperature did not rise above 90°. The reaction mixture was then poured into ice and water. Filtration and drying of the solid which precipitated gave 39.7 g. (93%) of an orange colored product m.p. 71.5–73°. Recrystallization from aqueous ethanol raised the melting point to 72.5–73.5°. Ramage and Trappe report m.p. 74–75° for this compound.[12]

Anal. Calcd. for $C_8H_{10}O_3N_2$: C, 52.7; H, 5.5; N, 15.4. Found: C, 53.0; H, 5.6; N, 15.3.

o-Amino-N-(2-hydroxyethyl)aniline. Fifty-one and seven-tenths g. (0.28 mole) of *o*-nitro-*N*-(2-hydroxyethyl)aniline, 24 ml. of 20% sodium hydroxide, and 120 ml. of 95% ethanol were heated to reflux on a steam bath with constant stirring. The source of heat was removed and 78 g. of zinc dust gradually added over a period of 45 min. Heating on the steam bath was then resumed and continued until the solution was colorless. The mixture was filtered rapidly with suction and the filtrate evaporated to dryness *in vacuo*. Eighty ml. of cold water was added to the residue and the undissolved solid filtered and dried, m.p. 101–104°. Recrystallization from water (Norit) gave 17.5 g. (40.6%) of diamine, m.p. 104.5–106.5°.

Ramage and Trappe[12] and Kremer[13] report m.p. 105–106° and 106–106.5°, respectively, for this compound.

Anal. Calcd. for $C_8H_{12}ON_2$: C, 63.1; H, 8.0; N, 18.4. Found: C, 63.4; H, 8.0; N, 18.6.

1-(2′-Hydroxyethyl)-2-(2′-pyridyl)benzimidazole (III). To 120 ml. of nitrobenzene containing 21.7 g. (0.2 mole) of pyridine-2-carboxaldehyde was added 30.4 g. (0.2 mole) of *o*-amino-*N*-(2-hydroxyethyl)aniline. The mixture was heated slowly during 1 hr. to the boiling point of the solvent and maintained at this temperature for 10 min. After cooling the reaction mixture overnight in an ice box the tan solid which separated was filtered and washed with 25 ml. of ether, yield 22.2 g. (47%), m.p. 126–127.5°. Two recrystallizations of the product from toluene (Norit) gave 18.0 g. (38%) of III, m.p. 129–129.8°. Further concentration of the mother liquors gave an additional 1.2 g. of a less pure material.

Anal. Calcd. for $C_{14}H_{13}ON_3$: C, 70.3; H, 5.5; N, 17.6. Found: C, 70.6; H, 5.6; N, 17.6.

6,7-Dihydrobenzimidazo[1,2-a]pyrido[2,1-c]pyrazinium bromide (IV). Eighteen g. (0.075 mole) of III was added to 230 ml. of 48% hydrobromic acid and the mixture refluxed for 4 hr. Evaporation of the acid solution to dryness and trituration of the residue with acetone gave 32.7 g. of an orange-brown solid. Two recrystallizations from aqueous ethanol gave 15.8 g. (70%) of a yellow solid melting at 341° with decomposition.

Anal. Calcd. for $C_{14}H_{12}N_3Br$: C, 55.6; H, 4.0; N, 13.9; Br, 26.5. Found: C, 55.9; H, 4.1; N, 13.9; Br, 26.5.

1,2,3,4,6,7-Hexahydro-13bH-benzimidazo[1,2-a]pyrido[2,1-c]pyrazine (V). Eight g. (0.027 mole) of IV was dissolved in 100 ml. of water and hydrogenated over 100 mg. of platinum oxide at an initial pressure of 48 p.s.i. After 30 min. the theoretical amount of hydrogen had been taken up and the catalyst was filtered. The colorless solution, which had been orange prior to reduction, was made strongly basic with 10% sodium hydroxide. Cooling and scratching induced crystallization of a colorless solid which was filtered and dried, 5.1 g., m.p. 158.5–160°.

Anal. Calcd. for $C_{14}H_{17}N_3$: C, 74.0; H, 7.5; N, 18.5. Found: C, 74.2; H, 7.3; N, 18.2.

1-(2′-Hydroxyethyl)-2-(3′-isoquinolyl)benzimidazole (VI). To 40 ml. of nitrobenzene containing 15.7 g. (0.1 mole) of isoquinoline-3-carboxaldehyde[14] was added 15.2 g. (0.1 mole) of *o*-amino-*N*-(2-hydroxyethyl)aniline and the mixture heated gradually during 1 hr. to the boiling point of the nitrobenzene. After maintaining the temperature at this point for 15 min., the solution was allowed to cool and was

(9) E. A. Steck, F. C. Nachod, G. W. Ewing, and N. H. Gorman, *J. Am. Chem. Soc.*, **70**, 3406 (1948).

(10) All melting points were done in open capillaries and are not corrected.

(11) Analyses were done by Micro-Tech Laboratories, Skokie, Ill.

(12) G. R. Ramage and G. Trappe, *J. Chem. Soc.*, 4406 (1952).

(13) C. B. Kremer, *J. Am. Chem. Soc.*, **61**, 1321 (1939).

(14) C. E. Teague, Jr., and A. Roe, *J. Am. Chem. Soc.*, **73**, 688 (1951).

stored overnight in an ice box. The precipitate which formed was filtered and washed with ether to give 10.7 g. of crude product, m.p. 136.5–138°. Several recrystallizations from toluene gave 6.3 g. (21.8%) of VI, m.p. 144.5–145.5°.

Anal. Calcd. for $C_{15}H_{15}ON_3$: C, 74.7; H, 5.2; N, 14.5. Found: C, 74.9; H, 5.3; N, 14.7.

Further cooling of the mother liquor from the reaction mixture gave a second crop of material which when recrystallized from toluene gave 4.1 g. of a yellow solid, m.p. 246.5–247°.

Refluxing this latter product with tetralin for 3 hr. left it unchanged. The product was not further characterized.

7,8-Dihydrobenzimidazo[1,2-a]isoquino[3,2-c]pyrazinium bromide (I). Two and nine-tenths g. (0.01 mole) of VI was added to 30 ml. of 48% hydrobromic acid and the mixture refluxed for 4 hr. The resulting dark red solution was evaporated to dryness. Trituration of the light tan residue with acetone gave 5.0 g. of crude product. Recrystallization from water gave 2.1 g. (60%) of the yellow quaternary salt, m.p. 347–348° with decomposition. The analytical sample was recrystallized again from water, m.p. 355–356° with decomposition.

Anal. Calcd. for $C_{18}H_{14}N_3Br$: C, 61.4; H, 4.0; N, 11.9; Br, 22.7. Found: C, 61.1; H, 4.1; N, 11.7; Br, 22.8.

5,6,7,8-Tetrahydro-14bH-benzimidazo[1,2-a]isoquino[3,2-c]pyrazine (VII). Three and seven-tenths g. (0.01 mole) of I was suspended in 200 ml. of water at 55°, and hydrogenated over 50 mg. of platinum oxide at an initial pressure of 47 p.s.i. After 2 hr. the hot solution was filtered and the filtrate made basic with ammonium hydroxide. The precipitate was filtered and dried, yield 1.9 g., m.p. 211–216°. Repeated recrystallizations from ethyl acetate gave the pure product, m.p. 221–223°.

Anal. Calcd. for $C_{18}H_{17}N_3$: C, 78.5; H, 6.2; N, 15.3. Found: C, 78.6; H, 6.2; N, 15.5.

2-(3′-Isoquinolyl)benzimidazole. Thirty and nine-tenths g. (0.2 mole) of isoquinoline-3-carboxaldehyde[14] and 21.2 g. (0.2 mole) of *o*-phenylenediamine were added to 80 ml. of nitrobenzene and the mixture gradually heated during 40 min. to the boiling point of the nitrobenzene. This temperature was maintained for 10 min., then the reaction mixture was allowed to cool. After standing overnight in an ice box the tan solid which separated was filtered and washed with benzene, yield 28.7 g. Recrystallization of the crude product from toluene gave 20.7 g., m.p. 193–194°.

Anal. Calcd. for $C_{16}H_{11}N_3$: C, 78.3; H, 4.5; N, 17.1. Found: C, 78.3; H, 4.6; N, 17.2.

Attempted alkylations of 2-arylbenzimidazoles. Attempts to alkylate 2-(2′-pyridyl)benzimidazole[8] with ethylene chlorohydrin in boiling toluene, with ethyl bromoacetate in absolute ethanolic potassium hydroxide at room temperature, or with allyl bromide in hot, absolute ethanolic sodium ethoxide were unsuccessful. The pyridylbenzimidazole was recovered from the reaction mixtures. 2-(3′-Isoquinolyl)-benzimidazole failed to give identifiable alkylation products with ethylene chlorohydrin in dioxane or with ethyl bromoacetate in hot, absolute ethanolic potassium hydroxide.

Absorption spectra. Ultraviolet absorption spectra were determined using a Beckman recording spectrophotometer, Model DK-2.

EAST LANSING, MICH.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MICHIGAN STATE UNIVERSITY]

Tetrazole Analogs of Aminobenzoic Acid Derivatives[1]

J. M. McMANUS[2,3] AND ROBERT M. HERBST

Received February 18, 1959

The three isomeric 5-nitrophenyltetrazoles and 5-(2′-hydroxy-4′-nitrophenyl)tetrazole have been prepared from the corresponding benzonitriles. Reduction of the 5-nitrophenyltetrazoles resulted in the formation of the corresponding 5-aminophenyltetrazoles which included the tetrazole analogs of *p*-aminobenzoic acid, *m*-aminobenzoic acid, and 2-hydroxy-4-aminobenzoic acid.

In recent years two aminobenzoic acid derivatives have been prominent in chemotherapy. *p*-Aminobenzoic acid plays a unique role in metabolism as a portion of folic acid, an essential material for the synthesis of nucleic acids. Evidence that certain drugs structurally related to *p*-aminobenzoic acid can inhibit its incorporation into folic acid[4] resulted in the application of the antimetabolite concept in chemotherapy as a means of combating bacterial invasion of the body. Those drugs which have been most effective in interfering with the utilization of *p*-aminobenzoic acid have been shown to be related to sulfanilamide[5] and have been used widely in the therapy of staphylococcal and pneumococcal infections. The second aminobenzoic acid derivative, important for its tuberculostatic activity,[6] is 2-hydroxy-4-aminobenzoic acid commonly referred to as *p*-aminosalicylic acid.

Because of the acidic nature of 5-substituted tetrazoles[7–9] the replacement of the carboxyl group of the aminobenzoic acids by the 5-tetrazolyl group should result in compounds of similar acidity and solubility. The possibility that the tetrazolyl analogs of the aminobenzoic acids might

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(1) Based on a thesis submitted to Michigan State University in 1958 by James M. McManus in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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(3) Present address: Chas. Pfizer & Co., Brooklyn, N. Y.

(4) D. Woods and P. Fildes, *Chem. and Ind. (London)*, **18**, 133 (1940).

(5) E. Northey, *The Sulfonamides and Related Compounds*, Reinhold Publishing Corp., New York, 1948.

(6) J. Lehmann, *Lancet*, **250**, 15 (1946).

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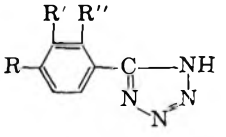
(9) R. M. Herbst and K. R. Wilson, *J. Org. Chem.*, **22**, 1142 (1957).

have useful therapeutic properties prompted investigation of their preparation.

Accordingly the preparation of the 5-nitrophenyltetrazoles necessary as intermediates was undertaken by two different techniques: first, the interaction of appropriate nitrobenzonitriles with hydrazoic acid in xylene solution; and second, interaction of the nitrobenzonitriles with sodium azide and acetic acid in refluxing *n*-butyl alcohol.[9] After completion of this work a procedure for the interaction of nitriles with ammonium or lithium azide in dimethylformamide appeared.[10] The new technique[10] permits much shorter reaction times.

Reduction of the nitrophenyltetrazoles to the corresponding aminobenzoic acid analogs was effected using either tin and hydrochloric acid as in the synthesis of 5-(3′-aminophenyl)- (I) and 5-(4′-aminophenyl)tetrazole (II) or hydrogen and platinum oxide as in the preparation of 5-(4′-aminophenyl)- and 5-(2′-hydroxy-4′-aminophenyl)tetrazole (III).



I. R, R″ = H; R′ = NH_2
II. R = NH_2; R′, R″ = H
III. R = NH_2; R′ = H; R″ = OH

The aminophenyltetrazoles possess amphoteric character; they are insoluble in cold water but readily soluble both in aqueous acids and alkalies. The acetyl derivatives used to characterize the aminophenyltetrazoles were prepared in glacial acetic acid solution with an equimolar amount of acetic anhydride.

Biological evaluation of the aminophenyltetrazoles is under way in the Research Laboratories of the Schering Corporation.

EXPERIMENTAL[11]

Preparation of Nitrophenyltetrazoles. 5-(3′-Nitrophenyl)-tetrazole. Procedure A. A mixture of 15.6 g. (0.11 mole) of *m*-nitrobenzonitrile and 50 ml. of xylene containing 6.8 g. of hydrazoic acid sealed in a Pyrex combustion tube was heated for 125 hr. at 140–145°. The contents of the tube were transferred to a flask and the tube washed with a small amount of warm benzene. Chilling the benzene-xylene mixture gave a crystalline product that was recrystallized from water using Norit to remove a trace of color, yield 8.6 g. (39%), m.p. 150.5–151.5°.

Anal. Calcd. for $C_7H_5N_5O_2$: C, 44.0; H, 2.6; N, 36.6. Found: C, 44.2; H, 2.7; N, 36.9.

Lossen[12] reported m.p. 145° for this compound.

Procedure B. A mixture of 32 g. (0.25 mole) of *m*-nitrobenzonitrile, 22 g. (0.34 mole) of sodium azide, and 20 g. (0.33 mole) of glacial acetic acid in 100 ml. of *n*-butyl alcohol was heated at reflux temperature for 4 days. An additional 5 g. of sodium azide and 10 g. of glacial acetic acid were added at this time and heating continued for 2 days. The reaciton mixture was diluted with 300 ml. of water and distilled until all the alcohol had been removed. Cooling and acidification of the residual solution caused separation of a pale yellow solid which was recrystallized from water using Norite to remove color. Yield 42 g. (88%) of product, m.p. 150.5–151.5°; mixture melting point with the material from procedure *A* was not depressed.

5-(2′-Nitrophenyl)tetrazole. Using procedure *A* the interaction of 25 g. (0.17 mole) of *o*-nitrobenzonitrile, 16.2 g. (0.25 mole) of sodium azide, and 15 g. (0.25 mole) of glacial acetic acid in 100 ml. of *n*-butyl alcohol gave 12.2 g. (38%) of 5-(2′-nitrophenyl)tetrazole. Recrystallization from water gave the pure product, m.p. 159.5–161°.

Anal. Calcd. for $C_7H_5N_5O_2$: C, 44.0; H, 2.6; N, 36.6. Found: C, 44.1; H, 2.8; N, 36.4.

5-(4′-Nitrophenyl)tetrazole. Following procedure *A* 15.6 g. (0.11 mole) of *p*-nitrobenzonitrile and 50 ml. of xylene containing 6.8 g. of hydrazoic acid gave 16.6 g. (77%) of product. The tetrazole was recrystallized from absolute ethanol, m.p. 218.5–219°. Pinner[13] reported m.p. 219° for this compound.

Anal. Calcd. for $C_7H_5N_5O_2$: C, 44.0; H, 2.6; N, 36.6. Found: C, 44.2; H, 2.7; N, 36.7.

Using procedure *B* 32 g. (0.25 mole) of *p*-nitrobenzonitrile, 22 g. (0.34 mole) of sodium azide and 22 g. (0.25 mole) of glacial acetic acid in 100 ml. of *n*-butyl alcohol gave 37 g. (78%) of 5-(4′-nitrophenyl)tetrazole. Recrystallization from water gave the pure product, m.p. 218.5–219°. A mixture melting point with the material from procedure *A* showed no depression.

5-(2′-Hydroxy-4′-nitrophenyl)tetrazole. A mixture of 41 g. (0 25 mole) of 2-hydroxy-4-nitrobenzonitrile,[14] 22 g. (0.34 mole) of sodium azide, and 22 g. (0.34 mole) of glacial acetic acid was heated at reflux temperature in 100 ml. of *n*-butyl alcohol for 6 days. The reaction mixture was diluted with 300 ml. of water and the mixture distilled until 250 ml. of distillate had collected. The solid which crystallized from the residual solution on cooling was recrystallized twice from water, yield 53.5 g. (94%). The analytical data indicate that this is the sodium salt of the desired tetrazole.

Anal. Calcd. for $C_7H_4N_5O_3Na$: N, 30.6. Found: N, 30.4.

The sodium salt was converted quantitatively into the free tetrazole by acidifying its hot aqueous solution to Congo red paper with concentrated hydrochloric acid. The free tetrazole was recrystallized from absolute ethanol, m.p. 283–283.5° with decomposition.

Anal. Calcd. for $C_7H_5N_5O_3$: C, 40.6; H, 2.4; N, 33.8. Found: C, 40.7; H, 2.8; N, 33.7.

Preparation of aminophenyltetrazoles. 5-(3′-Aminophenyl)-tetrazole (I). Concentrated hydrochloric acid (85 ml.) was added to a mixture of 17.2 g. of 5-(3′-nitrophenyl)tetrazole and 35 g. of granular tin in a 300 ml. 3-necked flask. The reaction started almost immediately and cooling was necessary. After stirring the mixture for an additional 15 min., the clear solution was decanted and the excess tin washed with a little water. The combined washings and acid solution were made basic with concentrated aqueous ammonia. The tin hydroxide was filtered and the filtrate acidified with glacial acetic acid until precipitation was complete. The colorless product, 11.5 g. (80%), was recrystallized from water, m.p. 199–200°.

Anal. Calcd. for $C_7H_7N_5$: C, 52.2; H, 4.4; N, 43.5. Found: C, 52.1; H, 4.5; N, 43.1.

5-(3′-Acetamidophenyl)tetrazole was obtained from I by interaction with acetic anhydride in glacial acetic acid. It separated from water as colorless crystals, m.p. 254–255° with decomposition.

(10) W. G. Finnegan, R. A. Henry, and R. Lofquist, *J. Am. Chem. Soc.*, **80**, 3908 (1958).

(11) Microanalyses were done on all compounds by Micro-Tech Laboratories, Skokie, Ill. Melting points were taken in open capillaries and are not corrected.

(12) W. Lossen and F. Statius, *Ann.*, **298**, 104 (1897).

(13) A. Pinner, *Ber.*, **27**, 990 (1894).

(14) J. McGhie, C. Morton, B. Reynolds, and J. Spence, *J. Soc. Chem. Ind.*, **68**, 328 (1949).

Anal. Calcd. for $C_9H_9N_5O$: C, 53.2; H, 4.5; N, 34.5. Found: C, 53.2; H, 4.6; N, 34.5.

5-(4'-Aminophenyl)tetrazole (II). (a) In a similar manner 17.2 g. of 5-(4'-nitrophenyl)tetrazole and 35 g. of granular tin were treated with 75 ml. of concentrated hydrochloric acid. II was isolated as in the preceeding preparation, yield 12.7 g. (88%), m.p. 267° with decomposition, after crystallization from aqueous ethanol.

(b) A suspension of 7.3 g. of 5-(4'-nitrophenyl)tetrazole in 150 ml. of glacial acetic acid was shaken with 150 mg. of platinum oxide catalyst at an initial hydrogen pressure of 49 p.s.i. After the theoretical amount of hydrogen had been absorbed, the chilled suspension of catalyst and product was filtered. The product was extracted from the mixture with hot ethanol and the solvent removed from the extract under reduced pressure. The residue was recrystallized from aqueous ethanol using Norit, yield 5.0 g. (82%), m.p. 267° with decomposition. Finnegan, Henry, and Lofquist[10] report m.p. 268–270° with decomposition.

Anal. Calcd. for $C_7H_7N_5$: C, 52.2; H, 4.4; N, 43.5. Found: C, 51.9; H, 4.3; N, 43.3.

5-(4'-Acetamidophenyl)tetrazole obtained from II with acetic anhydride in glacial acetic acid was recrystallized from glacial acetic acid with some difficulty. It separated as a colorless crystal powder, m.p. 278° with decomposition.

Anal. Calcd. for $C_9H_9N_5O$: C, 53.2; H, 4.5; N, 34.5. Found: C, 53.1; H, 4.7; N, 34.3.

5-(2'-Hydroxy-4'-aminophenyl)tetrazole (III). A suspension of 22.9 g. of the dry sodium salt of 5-(2'-hydroxy-4'-nitrophenyl)tetrazole in 150 ml. of water was shaken with 250 mg. of platinum oxide catalyst at an initial hydrogen pressure of 50 p.s.i. When hydrogen absorption was complete, the catalyst was filtered off and the filtrate warmed with a little sodium hydrosulfite to destroy a faint orange coloration. After treatment with Norit concentrated hydrochloric acid was added slowly to the cooled filtrate until no further precipitation occurred. The colorless, crystalline product was filtered off and dried, yield 13 g. (74%), m.p. 261–262° with decomposition.[15]

Anal. Calcd. for $C_7H_7N_5O$: C, 47.5; H, 4.0; N, 39.6. Found: C, 47.3; H, 4.2; N, 39.7.

5-(2'-Hydroxy-4'-acetamidophenyl)tetrazole was prepared from III by treatment with acetic anhydride in refluxing glacial acetic acid. It crystallized from water, in which it is difficultly soluble, as colorless needles, m.p. 281–282° with decomposition.

Anal. Calcd. for $C_9H_9N_5O_2$: C, 49.3; H, 4.1; N, 32.0. Found: C, 49.2; H, 4.3; N, 32.1.

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(15) B. Brouwer-van Straaten, D. Solinger, C. van de Westeringh, and H. Veldstra, *Rec. trav. chim.*, **77**, 1129 (1958)

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MICHIGAN STATE UNIVERSITY]

Alkylation Studies with Aminotetrazoles[1]

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Received March 3, 1959

A group of 1,4-disubstituted 5-iminotetrazolines has been prepared by alkylation of 1-cyclohexyl-, 1-cyclohexylmethyl- and 1-β-cyclohexylethyl-5-aminotetrazole with benzyl chloride, substituted benzyl halides and β-phenylethyl and γ-phenylpropyl bromide. The products were characterized as hydrochlorides and as substituted thioureas formed by interaction with phenyl isothiocyanate. A brief summary of their activity in microbiological systems is included.

Recently it was shown that 1,4-dialkyl-5-iminotetrazolines with a benzyl or substituted benzyl group in one position and a moderately large alkyl group, *n*-octyl for instance, at the other position exert a marked inhibitory action on growth of bacteria, protozoa, and fungi.[4,5] The purpose of the present investigation was to prepare a variety of 1,4-dialkyl-5-iminotetrazolines in which cyclohexyl or cyclohexylalkyl groups replaced the *n*-alkyl group. The resulting compounds were submitted for screening of their activity in microbiological systems; a brief summary of these results is included.

The iminotetrazolines were prepared by heating a mixture of the appropriate 1-cyclohexyl- or 1-cyclohexylalkyl-5-aminotetrazole with a small excess of benzyl, substituted benzyl, β-phenylethyl or γ-phenylpropyl halide. The iminotetrazoline hydrohalide so formed was subjected to steam distillation to remove excess aralkyl halide. Liberation of the base and extraction of the base with ether or benzene served to separate the product from unused 5-aminotetrazole derivative. The bases were converted into hydrochlorides as which they were isolated and characterized (Table I). The hydrochlorides are only very slightly soluble in water, moderately soluble in the common alcohols, but show the unique characteristic of rather marked solubility in hot benzene, toluene, or chloroform. The bases can be liberated from the hydrochlorides by shaking a suspension of the latter in dilute aqueous alkali and extraction with ether or benzene. Continuous removal of the coating of insoluble base from the sparingly soluble hydrochloride is essential for the success of the process. Many of the bases are viscous liquids; a few are solids and can be crystallized from cyclohexane (Table II). The

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(3) Present address: The Upjohn Company, Kalamazoo, Mich.

(4) R. M. Herbst and C. F. Froberger, *J. Org. Chem.*, **22**, 1050 (1957).

(5) T. F. Reutner, J. C. Peters, and E. F. Elslager, Abstracts of Papers presented at the 129th Meeting ACS, Dallas, Tex., April 1956, p. 7M.

bases react readily with phenyl isothiocyanate to form substituted thioureas which served to further characterize all the iminotetrazolines (Table III).

Structure assignment of the products is based on analogy of the method of preparation and upon characteristics of their infrared spectra. It has been shown[6,7] that alkylation of 1-substituted 5-aminotetrazoles under the conditions here employed results primarily in the formation of 1,4-dialkyl-5-iminotetrazolines. In one instance structure assignment has been verified experimentally. 1-β-Cyclohexylethyl-4-benzyl-5-iminotetrazoline was prepared both by benzylation of 1-β-cyclohexylethyl-5-aminotetrazole and by alkylation of 1-benzyl-5-aminotetrazole with β-cyclohexylethyl bromide. Hydrogenolytic removal of the benzyl group[8] from the latter product resulted in the formation of 1-β-cyclohexylethyl-5-aminotetrazole. The formation of the same product regardless of the order of introduction of the substituents and the result of the hydrogenolysis can be explained only if the two substituents are symmetrically placed in the 1 and 4 positions.[6,7]

Percival[9] has shown that infrared spectra of 1,4-dialkyl-5-iminotetrazoline hydrochlorides are characterized by strong absorption at about 5.95 μ and a notable absence of absorption at 2.9–3.2 μ and 3.7–4.4 μ, regions usually associated with N—H vibrations and amine hydrochlorides. 1-Alkyl-5-alkylaminotetrazole hydrochlorides can be distinguished from the isomeric 1,4-dialkyl-5-iminotetrazoline hydrochlorides by virtue of a strong and broad absorption band at 4.0–4.4 μ in the spectra of the former.[9] The iminotetrazoline hydrochlorides described in the present work uniformly show strong bands at about 3.4 μ and 6.0 μ, but no absorption at 2.9–3.2 μ or 3.7–4.4 μ. Percival also noted that 1,4-iminotetrazoline bases have a strong absorption band at 6.03 μ which is replaced by a band at 6.28 μ in spectra of the 1-alkyl-5-alkylaminotetrazoles. The free iminotetrazolines described here show strong bands at about 3.4 μ and 6.0 μ, but no absorption in the 6.3 μ region.

In addition the iminotetrazoline hydrochlorides have two peaks, one usually in the range 9.1–9.3 μ, the other around 9.5–9.6 μ, while the corresponding bases exhibit three peaks in the range 9.0–9.6 μ. These peaks may correspond to the absorption at about 9.4 μ shown by tetrazole itself and a number of 5-substituted tetrazoles which has been associated with the ring modes.[10] The possibility that absorption peaks in the 9.1–9.2 μ range shown by a number of 1,5-disubstituted tetrazoles is also associated with the ring modes has been suggested recently.[11]

The 1-cyclohexyl-, 1-cyclohexylmethyl- and 1-β-cyclohexylethyl-5-aminotetrazoles required were prepared from the appropriate primary amines by interaction in aqueous ethanol successively with cyanogen bromide and hydrazoic acid by adaptation of a procedure previously described for the preparation of 1-alkyl-5-aminotetrazoles.[4] The hydrazoic acid was liberated *in situ* from sodium azide. Cyclohexylmethylamine and β-cyclohexylethylamine were made from cyclohexylacetic acid and β-cyclohexylpropionic acid in 77% and 81% yields, respectively, by the Schmidt reaction.[12]

Microbiological screening was done in the Parke, Davis Laboratories; their cooperation is gratefully acknowledged.[13] Significant bacteriostatic activity measured by *in vitro* action on *Streptococcus pyogenes* appears uniformly in the cyclohexylethyl series (Compounds 19–27) all of which inhibit growth at concentrations of 20 γ per ml. or less. In the cyclohexylmethyl series only the mono- and dichlorobenzyl and the phenylpropyl derivatives (Compounds 11–14 and 18) are effective at this concentration, while in the cyclohexyl series only the *p*-chlorobenzyl derivative (Compound 3) is active at comparable concentrations. *In vitro* activity against *M. tuberculosis* (H 37 Rv) at levels of 10 γ per ml. or less was noted with Compounds 4, 5, 11–15, 18, 19, 26, and 27. None of the compounds was active against the same agents *in vivo*. Antitrichomonal action as measured *in vitro* against *Trichomonas vaginalis* is shown by almost all of the compounds at concentrations of 25 γ per ml. or less but is most marked in the cyclohexylethyl series where the *p*-chlorobenzyl derivative (Compound 21) is effective at concentrations as low as 1.6 γ per ml. All compounds were inactive *in vivo* against *Trichomonas fetus* in mice at levels up to 40 mg. per kg. per day. *In vitro* amebicidal activity was also apparent with most compounds and again most pronounced in the cyclohexylethyl series where Compounds 20, 26, and 27 were effective at concentrations of 20 γ per ml. *In vivo* amebicidal action was not realized. Pharmacodynamic effects such as hypotensive, analeptic, depressant, or diuretic action were absent when representative compounds were tested. Neither antiviral nor anticancer activity was observed with a few representative compounds selected for testing.

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(7) R. A. Henry, W. G. Finnegan, and E. Lieber, *J. Am. Chem. Soc.*, **76**, 2894 (1954).

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(13) Our thanks are due Drs. M. W. Fisher and P. E. Thompson of the Parke, Davis Laboratories for their kind cooperation.

EXPERIMENTAL[14]

Cyclohexylmethylamine. A 5-l. flask fitted with a reflux condenser, alcohol thermometer, stirrer, and 500-ml. dropping funnel, and set over a cold water bath that could be elevated or lowered easily, was charged with 213 g. (1.5 moles) of cyclohexylacetic acid, 2500 ml. of benzene, and 715 ml. of concentrated sulfuric acid. From the dropping funnel 475 ml. of a benzene solution of hydrazoic acid[15] (17.0 g. hydrazoic acid per 100 ml.) was added with vigorous stirring at a rate of about 3 ml. per min. The exothermic reaction which took place was controlled by keeping the reaction mixture at 42–48° by adjustment of the degree of immersion in the water bath. If the temperature falls too low, the reaction slows markedly and may stop. Should this occur, addition of hydrazoic acid solution should be interrupted immediately until the temperature can be raised and interaction again induced. After complete addition of the hydrazoic acid solution the mixture was maintained at 42–48° for 1 hr. by gentle warming on a steam bath with continued stirring. After cooling the reaction mixture in an ice bath, the layers were separated. The sulfuric acid layer was poured slowly, with stirring, into a 4-l. beaker filled with crushed ice. The dense precipitate of amine salt that formed was filtered rapidly with suction, pressed as dry as possible on the filter, and transferred immediately to a large flask. The salt was resuspended in a liter of water, treated with 600 g. of potassium hydroxide as 50% solution, and the liberated amine separated by steam distillation. The amine was separated from the distillate by extraction with ether. After drying the ether solutions over potassium carbonate, fractionation at atmospheric pressure gave 131 g. (77%) of cyclohexylmethylamine, b.p. 162–163°, n_D^{25} 1.4632.[17]

β-Cyclohexylethylamine was prepared in essentially the same manner. From 203 g. of β-cyclohexylpropionic acid, 134 g. (81%) of β-cyclohexylethylamine, b.p. 184–185°, n_D^{25} 1.4637[18] was obtained.

1-Cyclohexyl-5-aminotetrazole was prepared from cyclohexylamine by treatment successively with cyanogen bromide and hydrazoic acid in aqueous ethanolic solution, overall yield 62%, m.p. 217–218°. The procedure has been described previously in detail for other 1-alkyl-5-aminotetrazoles[4] and was adapted without significant change. The product was identical with a sample[19] prepared from cyclohexyl cyanide by the technique of von Braun and Keller.[20]

1-Cyclohexylmethyl-5-aminotetrazole. From 113 g. (1 mole) of cyclohexylmethylamine, 106 g. (1 mole) of cyanogen bromide, and 81 g. (1.25 moles) of sodium azide, following the technique used in the foregoing example, 145 g. (80%) of 1-cyclohexylmethyl-5-aminotetrazole was obtained, m.p. 250–251°.

Anal. Calcd. for $C_8H_{15}N_5$: C, 53.0; H, 8.3; N, 38.6. Found: C, 52.9; H, 8.3; N, 38.8.

The *acetyl* derivative, prepared by heating with acetic anhydride, was recrystallized from 50% ethanol, m.p. 129–130°.

Anal. Calcd. for $C_{10}H_{17}N_5O$: C, 53.8; H, 7.7; N, 31.4. Found: C, 53.7; H, 7.6; N, 31.4.

1-β-Cyclohexylethyl-5-aminotetrazole. From 127 g. (1 mole) of β-cyclohexylethylamine, 106 g. (1 mole) of cyanogen bromide, and 78 g. (1.2 moles) of sodium azide, following the procedure of the foregoing examples, 89 g. (47%) of 1-β-cyclohexylethyl-5-aminotetrazole was obtained. The product was recrystallized from 99% isopropyl alcohol, m.p. 212.5–213.5°.

Anal. Calcd. for $C_9H_{17}N_5$: C, 55.4; H, 8.8; N, 35.9. Found: C, 55.4; H, 8.5; N, 35.8.

The *acetyl* derivative, prepared by warming with acetic anhydride, was recrystallized from cyclohexane, m.p. 95.5–96.5°.

Anal. Calcd. for $C_{11}H_{19}N_5O$: C, 55.7; H, 8.1; N, 29.5. Found: C, 55.6; H, 8.0; N, 29.7.

5-Iminotetrazolines were prepared by interaction of 1-cyclohexyl-, 1-cyclohexylmethyl-, and 1-β-cyclohexylethyl-5-aminotetrazole with benzyl, substituted benzyl, β-phenylethyl and γ-phenylpropyl halides as previously described for similar compounds.[4] The preparation of 1-cyclohexyl-4 *p*-chlorobenzyl-5-iminotetrazoline hydrochloride will serve as a typical example. A mixture of 8.4 g. (0.05 mole) of 1-cyclohexyl-5-aminotetrazole and 12.1 g. (0.075 mole) of *p*-chlorobenzyl chloride was heated in an oil bath at 140°. A homogeneous melt formed during the first 0.5 hr. and resolidified slowly during the ensuing 0.5 hr. Heating was continued for 2 hr. after the melt had solidified completely. The crude hydrochloride was taken up in 200 ml. of hot 50% ethanol, the solution diluted with water, and steam distilled to remove ethanol and excess *p*-benzyl chloride. The residual aqueous suspension was treated with 4 g. of sodum hydroxide and shaken vigorously for 0.5 hr. Extraction with 3 portions of ether removed the free base. The combined ether solutions were dried over potassium carbonate. Evaporation of the solvent left the iminotetrazoline as a pale yellow oil which was taken up in 50 ml. of ethanol and treated with concentrated hydrochloric acid to precipitate the hydrochloride. The hot suspension was diluted with about 50 ml. of ethanol and 100 ml. of water to bring the hydrochloride into solution, treated with Norit and chilled. Recrystallization of the hydrochloride from 50% isopropyl alcohol gave 11.6 g. (70%) of pure product. Melting points, yields, and analytical data for all the iminotetrazoline hydrochlorides are given in Table I.

In a number of instances the free bases could be obtained as solids from the pure hydrochlorides by suspending the latter in 2*N* sodium hydroxide solution, shaking vigorously, and extracting the base with ether. Evaporation of the solvent after drying the ether solution over sodium sulfate left a solid in some instances, but more frequently a pale yellow oil that in a few cases could be induced to solidify on thorough chilling. Either cyclohexane or petroleum ether was used to recrystallize the solid bases. Melting points and analytical data for the bases are given in Table II.

Thiourea derivatives. All of the iminotetrazolines were characterized by formation of thiourea derivatives. The base liberated from 1 g. of hydrochloride suspended in aqueous sodium hydroxide was extracted with ether. The residual oil remaining after evaporation of the ether was warmed on a steam bath, without further purification, with phenyl isothiocyanate. After washing the crude thiourea derivatives with petroleum ether and 50% isopropyl alcohol, they were recrystallized from 75–80% isopropyl alcohol. In a few instances thorough chilling was necessary to induce crystallization of the crude thioureas. Melting points and analytical data for all the thioureas are recorded in Table III.

1-β-Cyclohexylethyl-4-benzyl-5-iminotetrazoline hydrochloride was prepared both by interaction of 1-β-cyclohexylethyl-5-aminotetrazole and benzyl chloride and by alkylation of 1-benzyl-5-aminotetrazole with β-cyclohexylethyl bromide. In the latter case the base was liberated from the crude hydrobromide and converted into the hydrochloride as described in the foregoing general procedure. The products prepared in both ways were identical. The iminotetrazoline hydrochloride (3.2 g.) obtained by alkylation of 1-benzyl-5-aminotetrazole was dissolved in 50 ml. of ethanol and shaken with 1 g. of 5% palladium-on-charcoal at an initial

(14) Microanalyses on all compounds were done by Micro-Tech Laboratories, Skokie, Ill. Melting points were done in open capillaries and are not corrected.

(15) Solutions of hydrazoic acid in benzene were prepared as previously described.[16] All work with hydrazoic acid must be done in a well ventilated hood.

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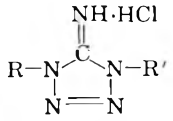
TABLE I

1,4-DISUBSTITUTED 5-IMINOTETRAZOLINE HYDROCHLORIDES

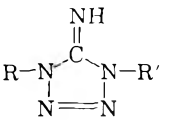


Compd. No.	R	R′	M.P., °C.[a]	Yield, %	Formula	Analyses							
						Calculated, %				Found, %			
						C	H	Cl	N	C	H	Cl	N
1	Cyclohexyl	Benzyl	230	72	$C_{14}H_{20}ClN_5$	57.2	6.8	12.1	23.8	56.9	6.8	12.2	23.6
2		*o*-Chlorobenzyl	222–223	54	$C_{14}H_{19}Cl_2N_5$	51.2	5.8	21.6	21.3	51.2	5.7	21.4	21.2
3		*p*-Chlorobenzyl	229–230	70	$C_{14}H_{19}Cl_2H_5$	51.2	5.8	21.6	21.3	51.2	6.0	21.6	21.4
4		2,4-Dichlorobenzyl	235–236	49	$C_{14}H_{18}Cl_3N_5$	46.4	5.0	29.3	19.3	46.4	5.1	29.4	19.3
5		3,4-Dichlorobenzyl	219–220	58	$C_{14}H_{18}Cl_3N_5$	46.4	5.0	29.3	19.3	46.3	5.0	29.3	19.3
6		*m*-Nitrobenzyl	217–218	64	$C_{14}H_{19}ClN_6O_2$	49.6	5.6	10.5	24.8	49.5	5.9	10.7	24.8
7		*p*-Nitrobenzyl	241–242	54	$C_{14}H_{19}ClN_6O_2$	49.6	5.6	10.5	24.8	49.8	5.7	10.3	24.8
8		β-Phenylethyl	220–221	53	$C_{15}H_{22}ClN_5$	58.5	7.2	11.5	22.8	58.6	7.2	11.5	23.0
9		γ-Phenylpropyl	222–223	54	$C_{16}H_{24}ClN_5$	59.5	7.5	11.0	21.7	59.6	7.6	11.3	21.3
10	Cyclohexylmethyl	Benzyl	217–218	61	$C_{15}H_{22}ClN_5$	58.5	7.2	11.5	22.8	58.7	7.2	11.5	22.6
11		*o*-Chlorobenzyl	234–235	58	$C_{15}H_{21}Cl_2N_5$	52.6	6.2	20.7	20.5	52.6	6.3	21.0	20.6
12		*p*-Chlorobenzyl	210–211	70	$C_{15}H_{21}Cl_2N_5$	52.6	6.2	20.7	20.5	52.8	6.2	20.7	20.6
13		2,4-Dichlorobenzyl	220	66	$C_{15}H_{20}Cl_3N_5$	47.8	5.4	28.2	18.6	48.1	5.6	28.3	18.9
14		3,4-Dichlorobenzyl	216	73	$C_{15}H_{20}Cl_3N_5$	47.8	5.4	28.2	18.6	48.1	5.4	28.2	18.7
15		*m*-Nitrobenzyl	218–219	65	$C_{15}H_{21}ClN_6O_2$	51.1	6.0	10.0	23.8	51.2	6.1	10.0	23.8
16		*p*-Nitrobenzyl	232	71	$C_{15}H_{21}ClN_6O_2$	51.1	6.0	10.0	23.8	51.2	5.9	10.1	23.9
17		β-Phenylethyl	234–235	67	$C_{16}H_{24}ClN_5$	59.7	7.5	11.0	21.8	59.5	7.3	11.2	22.0
18		γ-Phenylpropyl	240–241	69	$C_{17}H_{26}ClN_5$	60.8	7.8	10.6	20.8	60.6	7.9	10.7	21.1
19	Cyclohexylethyl	Benzyl	209–210	81	$C_{16}H_{24}ClN_5$	59.7	7.5	11.0	21.8	59.8	7.5	11.0	21.8
20		*o*-Chlorobenzyl	224–225	75	$C_{16}H_{23}Cl_2N_5$	53.9	6.5	19.9	19.7	54.0	6.4	19.7	19.7
21		*p*-Chlorobenzyl	208–209	81	$C_{16}H_{23}Cl_2N_5$	53.9	6.5	19.9	19.7	54.1	6.5	19.8	19.8
22		2,4-Dichlorobenzyl	210–211	74	$C_{16}H_{22}Cl_3N_5$	49.2	5.7	27.2	17.9	49.3	5.8	27.0	18.0
23		3,4-Dichlorobenzyl	208–209	71	$C_{16}H_{22}Cl_3N_5$	49.2	5.7	27.2	17.9	49.0	5.5	27.2	17.9
24		*m*-Nitrobenzyl	205–206	73	$C_{16}H_{23}ClN_6O_2$	52.4	6.3	9.7	22.9	52.5	6.4	9.8	22.9
25		*p*-Nitrobenzyl	210–211	58	$C_{16}H_{23}ClN_6O_2$	52.4	6.3	9.7	22.9	52.7	6.5	9.4	23.1
26		β-Phenylethyl	250–251	52	$C_{17}H_{25}ClN_5$	60.8	7.8	10.6	20.9	60.8	7.8	10.7	20.9
27		γ-Phenylpropyl	214–215	55	$C_{18}H_{28}ClN_5$	61.8	8.1	10.1	20.0	62.0	8.1	10.2	20.3

[a] All compounds melt with decomposition.

TABLE II

1,4-DISUBSTITUTED 5-IMINOTETRAZOLINES

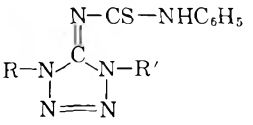


Compd.[a] No.	M.P., °C.	Formula	Analyses							
			Calculated, %				Found, %			
			C	H	Cl	N	C	H	Cl	N
10	93–94	$C_{15}H_{21}N_5$	66.4	7.8		25.8	66.4	7.8		25.7
12	82–83	$C_{15}H_{20}ClN_5$	58.9	6.6		22.9	58.3	6.7		23.1
13	103–104	$C_{15}H_{19}Cl_2N_5$	53.0	5.6	20.8	20.6	52.9	5.9	21.0	20.7
14	75–76	$C_{15}H_{19}Cl_2N_5$	53.0	5.6	20.8	20.6	53.0	5.7	20.7	20.7
15	90–91	$C_{15}H_{20}N_6O_2$	56.9	6.4		26.6	57.0	6.6		26.7
19	120–121	$C_{16}H_{23}N_5$	67.3	8.1		24.5				
20	58–59	$C_{16}H_{22}ClN_5$	60.1	6.9	11.1	21.9	60.2	7.1	11.3	21.7
21	53–54	$C_{16}H_{22}ClN_5$	60.1	6.9	11.1	21.9	59.9	6.8	11.3	21.7
22	70–71	$C_{16}H_{21}Cl_2N_5$	54.2	6.0	20.0	19.8	54.2	5.9	20.1	19.9
23	94–95	$C_{16}H_{21}Cl_2N_5$	54.2	6.0	20.0	19.8	54.3	6.1	20.0	19.8
24	84–85	$C_{16}H_{22}N_6O_2$	58.2	6.7		25.4	58.4	6.7		25.3
25	108–109	$C_{16}H_{22}N_6O_2$	58.2	6.7		25.4	58.1	6.9		25.6
26	50–51	$C_{17}H_{25}N_5$	68.2	8.4		23.4	68.2	8.2		23.2

[a] Numbers correspond with compounds described in Table I.

TABLE III

PHENYLTHIOUREAS DERIVED FROM 1,4-DISUBSTITUTED 5-IMINOTETRAZOLINES



Compd.[a] No.	M.P., °C.	Formula	Analyses					
			Calculated, %			Found, %		
			Cl	N	S	Cl	N	S
1	147–148	$C_{21}H_{24}N_6S$		21.4	8.2		21.2	8.0
2	135–136	$C_{21}H_{23}ClN_6S$	8.3	19.7	7.5	8.0	19.7	7.6
3	154–155	$C_{21}H_{23}ClN_6S$	8.3	19.7	7.5	8.1	19.5	7.4
4	121–122	$C_{21}H_{22}Cl_2N_6S$	15.4	18.2	7.0	15.2	18.5	7.0
5	188–189	$C_{21}H_{22}Cl_2N_6S$	15.4	18.2	7.0	15.4	18.5	6.9
6	174–175	$C_{21}H_{23}N_7O_2S$		22.4	7.3		22.7	7.2
7	161–162	$C_{21}H_{23}N_7O_2S$		22.4	7.3		22.7	7.3
8	106–107	$C_{22}H_{26}N_6S$		20.7	7.9		20.7	7.7
9	99–100	$C_{23}H_{28}N_6S$		20.0	7.6		20.0	7.8
10	174–175	$C_{22}H_{26}N_6S$		20.7	7.9		21.0	7.9
11	131–132	$C_{22}H_{25}ClN_6S$	8.0	19.1	7.3	8.0	19.3	7.0
12	156–157	$C_{22}H_{25}ClN_6S$	8.0	19.1	7.3	7.8	19.0	7.2
13	129–130	$C_{22}H_{24}Cl_2N_6S$	14.9	17.7	6.7	14.8	17.8	6.5
14	179–180	$C_{22}H_{24}Cl_2N_6S$	14.9	17.7	6.7	15.0	17.8	6.5
15	160–161	$C_{22}H_{25}N_7O_2S$		21.7	7.1		21.6	7.0
16	158–159	$C_{22}H_{25}N_7O_2S$		21.7	7.1		21.8	7.0
17	88–89	$C_{23}H_{28}N_6S$		20.0	7.6		20.2	7.5
18	117–118	$C_{24}H_{30}N_6S$		19.3	7.4		19.5	7.3
19	139–140	$C_{23}H_{28}N_6S$		20.0	7.6		20.0	7.3
20	118–119	$C_{23}H_{27}ClN_6S$	7.8	18.5	7.1	7.5	18.7	7.0
21	128–129	$C_{23}H_{27}ClN_6S$	7.8	18.5	7.1	7.7	18.6	7.1
22	115–116	$C_{23}H_{26}Cl_2N_6S$	14.5	17.2	6.6	14.3	17.3	6.6
23	144–145	$C_{23}H_{26}Cl_2N_6S$	14.5	17.2	6.6	14.3	17.3	6.6
24	129–130	$C_{23}H_{27}N_7O_2S$		21.1	6.9		21.2	7.0
25	134–135	$C_{23}H_{27}N_7O_2S$		21.1	6.9		21.0	6.9
26	86–87	$C_{24}H_{30}N_6S$		19.3	7.4		19.5	7.2
27	113–114	$C_{25}H_{32}N_6S$		18.7	7.2		18.7	7.1

[a] Numbers correspond to compounds described in Table I.

pressure of 50 p.s.i. Hydrogenolysis was complete in 0.5 hr. The catalyst was removed by filtration and washed with hot ethanol. The combined filtrate and washings were treated with 0.5 g. of sodium carbonate. Concentration of the solution gave 1.4 g. (71%) of 1-β-cyclohexylethyl-5-aminotetrazole, m.p. and mixture m.p. 212.5–213.5°.

Infrared spectra of the iminotetrazoline hydrochlorides and the corresponding bases were determined using a Perkin-Elmer double beam recording spectrophotometer, Model 21, and have been recorded.[21,22] All spectra were determined with oil mulls of the compounds at concentrations of the solid great enough to give strong absorption in the 6-μ region.

EAST LANSING, MICH.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF CONNECTICUT]

The Manganese Dioxide Oxidation of Allylic Alcohols

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Received January 16, 1959

It has been found that the rate and specificity of the manganese dioxide oxidation of allylic alcohols to allylic aldehydes is dependent on the quantity of oxidizing agent, the temperature, the solvent, and the method of preparation of the oxidizing agent. Allyl, benzyl, propyl, and isopropyl alcohols and *N*,*N*-dimethylaniline were oxidized with varying yields under different conditions and with a wide variety of manganese dioxides.

Manganese dioxide has been considered to be a specific reagent for the oxidation of allylic alcohols to allylic aldehydes and ketones. It has been used for the oxidation of vitamin A_1 and other polyene alcohols[2]; for unsaturated steroidal alcohols[3]; for α-santonins[4]; for alcohols in which an aromatic ring replaced the vinyl group[5]; for the determination of the stereochemistry of 10-hydroxycodeine derivatives[6]; for acetylenic alcohols[7]; and for ferrocene alcohols.[8]

The nonspecificity of manganese dioxide as an oxidizing agent for allylic alcohols has recently been reported. It was found to: oxidize primary and secondary amines to imine dimers in low yields,[9] 2 - hydroxytetrahydropyran to δ - valerolactone,[9] aniline to azobenzene,[10] *N*-methyl amines to *N*-formyl amines,[10] *N*-alkyl amines to the amine and the corresponding aldehyde from the alkyl group[10]; dehydrogenate an *N*-alkyl amine followed by oxidative cleavage of the enamine[10]; cleave tetrasubstituted ethylenediamines[10]; oxidize aliphatic primary and secondary alcohols to the corresponding aldehydes or ketones,[11] aldehydes to the acids,[11] and 1,2-glycols in steroids to give ketones and products resulting from bond cleavage[12]; and convert an allylic methylene group into an alcoholic or ketonic grouping.[13]

Several different types of manganese dioxide have been used for the above mentioned oxidations. The first was that of Ball, Goodwin, and Morton;[2b] followed by Attenburrow's "active" manganese dioxide;[2a] one by Rosenkranz, Sondheimer, and Mancera;[14] and two by Harfenist, Bavley, and Lazier,[5a] who reported one of their dioxides to be specific for benzyl type alcohols but unaffective on allyl alcohol.

The purpose of this research was to investigate the oxidation of allylic alcohols with the manganese dioxides mentioned above, others which had been reported in the literature, two commercial dioxides,

(1) Taken from the M.S. thesis of T.J.W., June 1958.

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TABLE I

OXIDATION OF ALLYL ALCOHOL[a]

Type of MnO_2	Petroleum Ether 5 g.	Petroleum Ether 10 g.	Petroleum Ether 15 g.	Chloroform 5 g.	Carbon Tetrachloride 5 g.	Benzene 5 g.	Ethyl Ether 5 g.
Attenburrow	99, 19 80, 2.0	92, 46		40, 1.0	66, 64	67, 1.0	75, 0.2
Ball, Goodwin, and Morton	90, 0.5	97, 0.1		1, 4.5	50, 0.2	56, 2	64, 0.2
Glemsir (No. 1)[b]		5, 22	100, 17	20, 25	45, 1.0	50, 1.0	69, 0.2
Glemsir (No. 2)[b]	89, 0.75	97, 0.5					
Harfenist, Bavley, and Lazier (No. 1)	92, 1.5	97, 0.1		81, 29.4	50, 1.0	67, 1.0	81, 19
Harfenist, Bavley, and Lazier (No. 2)	82, 1.5	89, 1.0					
Maxwell, Thirsk, and Butler (No. 1)		80, 22	100, 1.0	18, 20.7	48, 2	53, 0.2	59, 0.2
Maxwell, Thirsk, and Butler (No. 2)		40, 23	100, 17	17, 19.3	38, 2	56, 0.2	69, 0.2
Maxwell, Thirsk, and Butler (No. 3)	48, 19.5	96, 0.2					
Rosenkranz, Sondheimer, and Mancera		31, 46	100, 70	12, 19.5	34, 0.2	55, 2.5	82, 0.2
Baker Analyzed (commercial)		32, 50	41, 16	12, 20	34, 0.2	50, 0.2	78, 0.2
Baker & Adamson (commercial)	99, 19	92, 0.7		22, 26	51, 3	52, 0.2	82, 0.2
Pyrolysis of manganous nitrate	40, 57			15, 10.5	39, 0.2	55, 1.0	83, 18
Electrolysis of manganous nitrate	80, 38			22, 24.5	53, 23	61, 0.2	59, 0.2
Manganous chloride and hydrogen peroxide	39, 57			1, 10.5	32, 3	53, 0.2	88, 0.2
From manganous acetate	92, 57						
Potassium permanganate refluxed in methanol and petroleum ether	42, 24.5						
From barium permanganate	70, 24						
From manganous chromate	95, 29						
Attenburrow[c]	89, 42						
Attenburrow[d]	48, 23						
Attenburrow[e]	85, 45						
Attenburrow[f]	48, 45						
Attenburrow[g]	75, 24						
Attenburrow[h]	34, 26						
Attenburrow[i]	45, 20						
Attenburrow[j]	37, 20						
Attenburrow[k]	35, 22.6						

[a] All oxidations were done with 50 g. of a 2% by weight solution. The first number in the columns indicates the per cent yield, and the second the time in hours. The numbers which follow the types of manganese dioxides indicate the order of preparation of the dioxides in the original article. [b] O. Glemsir, *Ber.*, **72B**, 1879 (1939). [c] Washed with 15% nitric acid [d] Washed with methanol and ether and dried at 130°. [e] Washed with water and dried at 120°. [f] Dried at 220–280°. [g] Refluxed in hydrochloric acid and reoxidized with chlorine. [h] Refluxed in methanol and ether and dried at 100°. [i] 3 g. of the dioxide was used. [j] 1 g. of the dioxide was used. [k] 0.5 g. of the dioxide was used.

those prepared by pyrolysis and electrolysis, and with other oxidizing agents on manganous compounds. The latter dioxides were prepared by methods which did not utilize permanganate and hence were an attempt to prepare manganese dioxide free from permanganate.

These dioxides were used to determine: (1) the time needed for complete oxidation or when the oxidation stopped, (2) the effect of solvent, (3) the quantity of oxidizing agent required for efficient oxidation, and (4) the effect of washing and drying the precipitated manganese dioxide in various ways. These results have been summarized in Table I, where the yields indicate the total amount of aldehyde produced, although the extent of oxidation was determined at various time intervals (approximately 10 minutes, 30 minutes, 1 hour, 20 hours, and 60 hours) until the oxidation was complete.

Table II depicts the rate of oxidation with three different preparations of manganese dioxide at room temperature and the absence of any change in rate when the temperature is raised by 25°. In addition, it was found that air oxidation was not important for the rate and extent of oxidation did not change in a nitrogen atmosphere.

The manganese dioxide oxidation of benzyl, propyl, and isopropyl alcohols and *N*,*N*-dimethylaniline in representative solvents is summarized in Table III.

All of the oxidations were followed by infrared analysis of a 2% solution of the alcohols and amine in neutral solvents. When an alcohol was studied, the rate was measured by the gradual decrease of the

TABLE II

EFFECTS OF TEMPERATURE AND ATMOSPHERE[a]

Type of MnO_2	Normal	Nitrogen Atmosphere	40° ± 0.2°	45° ± 0.2°	50° ± 0.2°	66° ± 1°
Attenburrow	51, 0.12	48, 0.12				
	65, 0.5	53, 0.7				
	80, 1.0	89, 13				
	99, 19					
Ball, Goodwin, and Morton	85, 0.12	70, 0.12				
	90, 0.5	70, 0.7				
	92, 0.75					
Rosenkranz, Sondheimer, and Mancera	22, 6[b]	30, 0.18	30, 0.18	35, 0.18	34, 0.12	31, 0.12
	31, 46	32, 1.7	43, 11.25	42, 10.75	41, 10.25	89, 10.5
		36, 29	45, 23	44, 25.7	43, 24.5	100, 26
Pyrolysis of manganous nitrate	0, 0.18		28, 0.18	22, 0.18	32, 0.18	17, 0.21
	14, 1.5		32, 11.75	30, 12	37, 10	43, 15.7
	21, 6		43, 25.25	38, 24	45, 27	49, 23.25
	40, 57					92, 36.75

[a] 5 g. of MnO_2 was used. The first number indicated per cent yield and the second the time in hours. The temperature was controlled with a Thermocap Relay. [b] 10 g. of MnO_2 was used.

TABLE III

OTHER OXIDATIONS WITH 5 G. OF MnO_2[a]

Compound	Benzyl Alcohol		1-Propanol		2-Propanol	*N,N*-Dimethyl aniline
Solvent	Petroleum Ether	Carbon Tetrachloride	Petroleum Ether	Carbon Tetrachloride	Carbon Tetrachloride	Carbon Tetrachloride
Type of MnO_2						
Attenburrow	63, 2.7	69, 4.3	13, 30	78, 47	62, 26	45, 33.5
Ball, Goodwin, and Morton	60, 2.7	49, 4	17, 29	22, 47	38, 26	18, 31.5
Electrolysis of manganous nitrate	62, 2.7	71, 20	25, 29	58, 47	31, 26	13, 32.5
Glemsir (No. 1)	67, 0.1	56, 20	30, 25	28, 47		
Rosenkranz, Sondheimer, and Mancera	60, 2.7	52, 3.7	5, 30	27, 47		
Pyrolysis of manganous nitrate	60, 2.7	50, 0.2	5, 29	26, 47		
Attenburrow[b]			25, 36.5	40, 26	92, 26	

[a] The first number indicates the per cent yield and the second indicates time in hours. [b] 10 g. of the dioxide was used.

oxygen-hydrogen peak at 3.0 microns, and the rate of amine oxidation was determined by the decrease of the carbon-hydrogen peak at 3.5 microns. This was possible, since it was determined that both the oxygen-hydrogen and carbon-hydrogen peaks were inversely proportional to the carbonyl peak.

Discussion of Results. The results of this study are not in complete agreement with those reported previously. In many cases these discrepancies can be attributed to differences in experimental techniques. The excellent yields obtained in the short times are possibly due to an improvement in technique. All reaction mixtures were stirred continuously with a Teflon-covered stirring bar and magnetic stirrer. This permits a constant change in the surface of the manganese dioxide and enabled the unoxidized portion of the alcohol in solution to make contact with the surface of the dioxide. Previous techniques placed the alcohol and solvent in a stoppered flask which contained the manganese dioxide, and the reaction mixture was agitated at different time intervals. A good yield of product required six to twelve days.

The data in Table I indicates that some manganese dioxides give efficient oxidation of allyl alcohol in petroleum ether when 10 g. of the dioxide (to 1 g. of alcohol) is used in one half to twenty-four hours. The initial rate is decreased when 5 g. of oxidant is used, but comparable yields can still be obtained in approximately the same time. Further decrease in the quantity of dioxide resulted in diminished oxidation. Other dioxides failed to give efficient oxidation when 10 g. was used. When the amount of oxidizing agent was increased to 15 g., a comparable yield of acrolein was obtained. These results clearly prove the previous suggestion of Henbest[10] that the yield of aldehyde depends on the quantity of oxidizing agent. In addition the rates of oxidation have been determined (Table II).[1]

The dioxides which give rapid oxidation and high yields utilize permanganate or chromate in their preparation. This suggests the presence of permanganate or other higher oxidation states of manganese or chromium which are absorbed and occluded when the manganese dioxide is precipitated. Other evidence for possible permanganate oxidation is indicated by the fact that the dioxides which utilized no permanganate in their preparation failed to give a large yield of acrolein in the early stages of oxidation. Attempts to detect the presence of permanganate by x-ray and ultraviolet analysis were unsuccessful.

A procedure was utilized to remove any adsorbed or occluded permanganate and other manganese oxides from two dioxides and the results indicate that the oxidation rate in the early stages of reaction is decreased appreciably. When 25- and 100-mg. samples of potassium permanganate were added to 5 g. of dioxide the initial oxidation rate showed a slight increase. The present study has revealed that washing and drying of the precipitate exerts an influence on the oxidizing power of the dioxide. When the precipitate is washed with organic solvents the yield is lowered, possibly because any adsorbed permanganate or other species which cause rapid oxidation are removed to a greater extent by the organic solvent than by water. This could reduce the oxidizing power of the dioxide. Thus, the manganese dioxide which was prepared from potassium permanganate refluxed in petroleum ether and methanol, showed poor initial oxidation and a comparatively low yield of acrolein after twenty-four hours of reaction. Washing with nitric acid does not appear to have any appreciable effect, but drying at high temperature causes a decrease in oxidizing power. This result substantiates Henbest's[10] and Evans'[15] statements that the manganese dioxide must be partially hydrated for efficient oxidation.

Attenburrow stated that the oxidizing power of his dioxide was due to precipitation in an alkaline media.[2a] This is inconsistent with the results of this study, since effective dioxides which utilized permanganate in their preparations were precipitated either from neutral or acid media.

The dioxides prepared from manganous chloride and hydrogen peroxide, the electrolysis and pyrolysis of manganous nitrate, and manganous acetate and ammonium persulfate are essentially free from permanganate contamination. The present results indicate that the initial rate of oxidation is considerably less in comparison to the dioxides which appear to be contaminated by permanganate. The yields of acrolein after fifty-seven hours of oxidation are also lower.

The possibility of air oxidation in the reaction was investigated by conducting the oxidations in an atmosphere of nitrogen. The results imply that air oxidation is negligible.

The results of the temperature study on the oxidation of allyl alcohol appear in Table II. The results between 40°, 45°, and 50° would indicate that there is no Arrhenius temperature effect. When the oxidation was carried out at reflux temperature (63°), the oxidizing power of these two dioxides was increased by approximately 60% over the normal rate indicating a definite increase in oxidation when there is a sufficient increase in the temperature.

The effect of solvent on the oxidation rate was extensively investigated with a variety of dioxides. The results indicate that the extent of oxidation is reduced from 50 to 70% when chloroform or carbon tetrachloride is used in place of petroleum ether and that the dioxides which show possible permanganate contamination are affected more than the dioxides which are essentially permanganate free. In benzene the effect is not so pronounced, for the oxidation rate is decreased by 20 to 30%. In ether, all the dioxides gave increased yields, but these results are not accurate since the high volatility of ether hindered quantitative measurements.

The present investigation was also extended to another allylic alcohol, benzyl alcohol. The results in Table III indicate that the yields of benzaldehyde in petroleum ether, though less than acrolein, are about 65% after three hours of oxidation when the benzyl alcohol is present in about one half the concentration of allyl alcohol. The simultaneous increase of the hydroxyl and carbonyl peaks in the infrared suggests some oxidation to benzoic acid. The results in carbon tetrachloride are comparable to those of allyl alcohol in the same solvent, which indicates that there are several inconsistencies with those communicated in the literature. Turner[5b] attempted the oxidation of benzyl alcohol with the dioxide of Rosenkranz, Sondheimer, and Mancera[14] and reported that the alcohol could not be oxidized. The present study shows a 60% yield of benzaldehyde is obtained after three hours with the same dioxide.

Padilla and Herran[12] tested the oxidizing power of several dioxides and their findings indicated the dioxide of Rosenkranz, Sondheimer, and Mancera[14] to be the most efficient. The present results indicate the dioxides of Attenburrow[2a] and of Ball, Goodwin, and Morton[2b] to be superior to that of Rosenkranz, Sondheimer, and Mancera in the oxidation of benzyl and allyl alcohol.

Dissimilarities also occur with the results of Harfenist, Bavley, and Lazier.[5a] These investigators found that their dioxide (No. 1) would oxidize benzyl alcohol to benzaldehyde, but would not oxidize allyl alcohol to acrolein. This study indicates that the dioxide (No. 1) is more efficient for the oxidation of allyl alcohol than (No. 2).

(15) R. M. Evans, *Proc. Chem. Soc.*, 47 (1958).

The specificity of manganese dioxide for allylic alcohols was investigated with 1-propanol, 2-propanol, and *N*,*N*-dimethylaniline. The results in Table III indicate that nonallylic compounds can be oxidized with manganese dioxide, but usually not so well as allylic compounds. This is in excellent agreement with the findings of Abel-Wahab, El-Sadr, and Barakat[11] and the results of Highet and Wildman.[9]

The present results do not permit us to make any definite statements about the mechanism of this oxidation. Several pertinent facts are evident: Allyl and benzyl alcohols are oxidized more readily than saturated alcohols, which would indicate that the π-electrons of the double bond have some affect; allyl alcohol is oxidized more readily than benzyl alcohol, which might indicate a steric effect; and Rapoport[6] has found that *cis*-10-hydroxydihydrodesoxycodeine is oxidized more readily than the *trans* alcohol. One aspect which hinders the clarification of this oxidation is that the fate of the manganese dioxide is not known. It is anticipated that future work will permit us to clarify some of the mechanistic aspects of the reaction.

EXPERIMENTAL

Reagent. The following reagents were used in the preparation of the manganese dioxides: manganous chromate (British Drug House), manganous sulfate (Baker and Adamson), manganous acetate (Fisher Analytical Reagent), manganous nitrate (Mallinckrodt), manganous chloride (Mallinckrodt), barium permanganate (British Drug House), potassium permanganate (Baker and Adamson), ammonium persulfate (Baker and Adamson), manganous carbonate (Baker Analyzed Reagent), manganous oxalate (British Drug House), and hydrogen peroxide (30%, Baker and Adamson).

The following materials were distilled through a 16-in. silvered column packed with glass helices: petroleum ether (Fisher White Label, b.p. 63–64°), which was dried for 12 hr. over sodium sulfate, carbon tetrachloride (Baker and Adamson, b.p. 76–77°) which was washed with concentrated sulfuric acid and water and dried over a mixture of sodium sulfate and Drierite, chloroform (Baker and Adamson, b.p. 58–60°) which was washed with concentrated sulfuric acid and water and dried over a mixture of sodium sulfate and Drierite, allyl alcohol (Eastman White Label, b.p. 96–97°, n_D^{20} 1.4135), benzyl alcohol (Eastman Yellow Label, b.p. 76.7° at 4.5 mm., n_D^{20} 1.5395), 1-propanol (Eastman White Label, b.p. 97–98°, n_D^{20} 1.3854), 2-propanol (Mallinckrodt, b.p. 82–83°, n_D^{20} 1.3776), and *N*,*N*-dimethylaniline (Fairmount Chemicals, b.p. 72° at 3.8 mm., n_D^{20} 1.5582). Acrolein (Eastman Yellow Label, b.p. 52.5°) was distilled through a small Claisen apparatus and immediately added to petroleum ether to retard polymerization.

Variations in preparation of manganese dioxides reported in the literature. The following variations were performed on manganese dioxide prepared by the method of Attenburrow: (1) It was washed with 15% nitric acid and dried at 220° to 280° according to the method of Harfenist, Bavley, and Lazier;[5a] (2) It was washed with methanol and ether and dried at 130° by the method of Rosenkranz, Sondheimer, and Mancera;[14] (3) It was dried at 120° after washing with water; (4) It was dried at 220° to 280°; (5) Manganese dioxide (50 g.) was refluxed in 100 ml. of concentrated hydrochloric acid until it was reduced to manganous chloride (green coloration of solution). This also reduced any permanganate which was present. The solution was then neutralized with concentrated sodium hydroxide, while the manganous chloride solution was stirred in an ice bath. Chlorine gas (purified with sulfuric acid) was admitted into the solution and oxidized the manganese back to the plus four state. The manganese dioxide was washed with 3 l. of water and dried at 100° for 2 days; (6) Manganese dioxide (50 g.) was added to a solution of 50 ml. of methanol and 50 ml. of petroleum ether, and refluxed for 24 hr. The manganese dioxide was dried between 80° and 100° for 2 days.

The following variations were performed on manganese dioxide prepared by the method of Ball, Goodwin, and Morton[2b]: (1) It was reduced to manganous chloride and reoxidized to the plus four oxidation state with chlorine; (2) It was washed with methanol and ether and dried at 130° by the method of Rosenkranz, Sondheimer, and Mancera.[14]

The dioxide of Rosenkranz, Sondheimer, and Mancera[14] was refluxed in methanol and petroleum ether for 24 hr. and dried between 80° and 100° for 2 days.

Other methods used in the preparation of manganese dioxide. A. Preparation of manganese dioxide from manganous acetate. Manganous acetate (114.2 g.) was dissolved in 2 l. of water to which 200 ml. of sulfuric acid (2*N*) were added. The solution was heated to boiling and ammonium persulfate (226 g.) was added over a 30-min. period. The manganese dioxide precipitated after 15 min. It was filtered, washed with water till the washings were neutral, and dried at 60° for 2 days.

B. Preparation of manganese dioxide from pyrolysis of manganous nitrate. Manganous nitrate was heated gradually to 400° and maintained at 400° for 1 hr. The manganese dioxide was then washed with water (1 l.) and dried at 60° for 2 days.

C Preparation of manganese dioxide from electrolysis of manganous nitrate. Equal volumes of concentrated nitric acid and manganous nitrate were placed in a 1-l. vessel. Two platinum electrodes connected to a 6-volt transformer were placed in the solution and the current turned on low until the decomposition voltage was reached. Complete deposition of manganese dioxide took 3–4 days. The manganese dioxide was filtered, washed with water until the washings were neutral, and dried at 60° for 2 days.

D. Preparation of manganese dioxide from potassium permanganate. Potassium permanganate (25 g.) was added to a solution of 300 ml. of methanol and 100 ml. of petroleum ether and the resulting mixture was refluxed with stirring for 2 days. The permanganate was reduced to manganese dioxide which was filtered, washed with water until the washings ran clear, and dried at 60° for 2 days.

E. Preparation of manganese dioxide from manganous chloride. Manganous chloride (300 g.) was dissolved in 2 l. of water. The solution was made slightly alkaline by addition of sodium hydroxide (6*N*). Hydrogen peroxide (453 g. of a 30% solution) was then added with a dropping funnel for 1.5 hr. and the solution was stirred at 10-min. intervals. The brown manganese dioxide was collected by filtration, washed with water until the washings were neutral, and dried at 60° for 2 days.

F. Preparation of manganese dioxide from barium permanganate. Barium permanganate (453 g.) was dissolved in water (1 l.) and 300 ml. of sulfuric acid (concentrated) was added slowly with stirring. The permanganate was reduced to manganese dioxide which was collected by filtration, washed with water until the washings were clear, and dried at 60° for 2 days.

G. Preparation of manganese dioxide from manganous chromate. Manganous chromate (50 g.) was dissolved in 1 l. of water. 100 ml. of 2*N* sulfuric acid was added, and the solution was heated to boiling. Ammonium persulfate (113 g.) was added over a period of 0.5 hr. to the hot solution. The black manganese dioxide was collected by filtration, washed with hot water till the washings were clear (6 to 7 l.), and dried at 60° for 2 days.

Construction of the infrared standardization curves. Accurately weighed amounts of the four alcohols, acrolein, and the tertiary amine were added to 49 g. of the appropriate solvent to give the required percentage solution. The infrared spectra (Perkin-Elmer Model 21) of the solutions were obtained in a 0.5-mm. sodium chloride absorption cell with a reference of solvent in a 0.5-mm. cell. This method gave excellent resolution of the peaks due to oxygen-hydrogen stretching at 3.00 microns in the alcohols, carbon-oxygen double bond stretching at 5.85 microns in the aldehydes, and the carbon-hydrogen stretching at 3.50 microns in the amine. The percentage transmissions of the oxygen-hydrogen, carbon-oxygen double bond, and the carbon-hydrogen peaks were determined for the various concentrations, and these were plotted against concentration to give the standardized curves. The curves showed both positive and negative deviations from Beer's Law, but subsequent determinations indicated that the curves were accurate to ±2%.

Methods used in this study. One-gram samples of the four alcohols and *N,N*-dimethylaniline were weighed in a weighing bottle. The solvent (49 g.) and the manganese dioxide were weighed on a triple beam balance and placed in a flask equipped with a condenser and a sidearm that permitted samples to be taken. The compound was transferred from the weighing bottle to the flask with a hypodermic syringe. The reaction mixture was stirred with a Teflon-covered stirring bar and a magnetic stirrer. At the desired time stirring was stopped, the rubber bulb capping the sidearm was removed, and a sample was taken with a hypodermic syringe and transferred to the infrared cell. The per cent transmission of the sample was then determined.

When the reaction was carried out in a nitrogen atmosphere, a hypodermic needle which extended below the surface of the reaction mixture was pushed through the rubber bulb on the sidearm. Nitrogen was then passed through the solution for 0.5 hr. to remove the air present. The condenser was equipped with a mercury bubbler which was then closed to prevent air from entering the system. Samples were taken with a hypodermic syringe through the rubber bulb covering the sidearm.

In those reactions carried out at elevated temperatures a flask with a sidearm and a thermometer well was used. The reaction mixture was prepared in the usual manner. The temperature was controlled to ±0.2° by a Thermocap Relay (Niagara Electron Laboratories) which was attached to a thermometer placed in the thermometer well of the flask, which was heated with a heating mantle. To ensure better thermal conductivity some mercury was placed in the thermometer well. The samples were obtained in the same manner as above.

X-ray study. An attempt was made to detect traces of the suspected permanganate in the dioxide of Attenburrow; Ball, Goodwin, and Morton; Maxwell, Thirsk, and Butler (No. 3); Baker Analyzed (Commercial); Glemsir (No. 2); and the dioxide prepared from the pyrolysis of manganous nitrate, by x-ray diffraction. An x-ray diffraction pattern (Phillips Standard Unit with Cu radiation) was first taken of potassium permanganate and this was used as a standard. The lines on the x-ray pictures of the above dioxides did not show any similarity to the lines produced by the potassium permanganate. In many instances the lines were blurred and this is in agreement with the analysis reported by Maxwell, Thirsk, and Butler[16] who obtained dark brown pictures. The x-ray information is limited since it is difficult to detect materials present in concentrations of less than 5%.[17]

Ultraviolet study in the visible range. An attempt was made to detect the suspected permanganate in the above manganese dioxides with an ultraviolet spectrophotometer (Beckman Model DU). A preliminary study was made on permanganate in a mineral oil suspension, and it was found that absorption occurred between 540 and 545 mμ. The samples were prepared by suspending 100 mg. of the dioxides in 2.97–3.00 g. of mineral oil. The dioxides failed to give any absorption in the permanganate region, but this could be due to the inability of the apparatus to detect traces of permanganate present in concentrations less than 2%.[18]

Acknowledgment: The authors are indebted to Dr. R. K. Murmann for his assistance in the attempts to prepare "pure" manganese dioxide. The infrared spectrophotometer which was used was purchased with funds from a research grant to the University (N.S.F.-G 2369).

STORRS, CONN.

(16) K. H. Maxwell, H. R. Thirsk, and G. Butler, *J. Chem. Soc.*, 4210 (1952).

(17) C. W. Bunn, *Chemical Crystallography*, The Clarendon Press, Oxford, 1946, pp. 125–6.

(18) Private communication, Dr. W. C. Purdy, Dept. of Chemistry, University of Maryland.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Structure and Antimicrobial Activity of the 3-Aminorhodanines

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Received January 19, 1959

Some *N*-substituted derivatives of 3-aminorhodanine have been synthesized by the cyclization of the corresponding carboxymethyl dithiocarbazates and their structures confirmed by infrared and ultraviolet spectra. Within this series, the most active compounds in producing inhibition of the growth of *A. niger* are the *p*-haloanilinorhodanines.

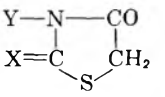
The antimicrobial activity[1] of the 3-phenyl- (IA) and 3-benzylrhodanines (IB) suggested the investigation of other 3-substituted rhodanines. By the principle of isosterism,[2] the 3-anilinorhodanines (IC) would be expected to resemble the 3-benzylrhodanines in activity. It was also anticipated that the presence of the amino group would perhaps lead to the possibility of salt formation and hence greater water solubility, since 3-amino-2,4-thiazolidine (ID) has been isolated as a hydrochloride salt.[3]

(1) F. C. Brown, C. K. Bradsher, E. C. Morgan, M. Tetenbaum, and P. Wilder, Jr., *J. Am. Chem. Soc.*, **78**, 384 (1956).

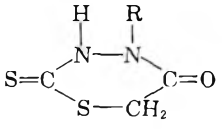
(2) H. Erlenmeyer, *Bull. soc. chim. biol.*, **30**, 792 (1948).

(3) H. W. Stephen and F. J. Wilson, *J. Chem. Soc.*, 2531 (1926).

3-Amino- (IE)[4b,c] and 3-anilinorhodanine (IC)[4a,c] were reported about fifty years ago; the former melts at 92°, the latter at 133.5–134°. By the same procedure, Mathes[5] obtained compounds with the same melting points, but he formulated the products as derivatives of the six-membered 1,3,4-thiadiazine structure, IIA and IIB. Such compounds would be expected to tautomerize to the thioenol form and be soluble in base. Diacetyl derivatives of the compound melting at 92° have been prepared,[6] but it is obvious that either structure (IE or IIA) would be expected to form a diacetyl derivative.



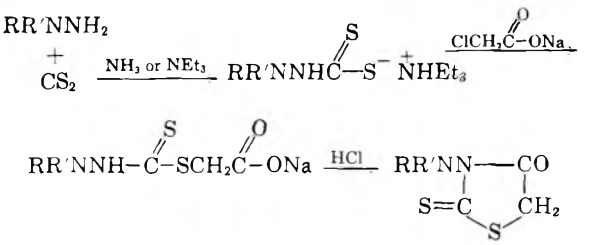
IA. X = S; Y = C_6H_5
IB. X = S; Y = $CH_2C_6H_5$
IC. X = S; Y = NHC_6H_5
ID. X = O; Y = NH_2
IE. X = S; Y = NH_2
IF. X = S; Y = $N(CH_3)_2$



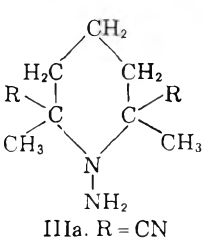
IIA. R = H
IIB. R = C_6H_5

Chemical evidence in favor of the 3-aminorhodanine structure has been reported recently,[7,8] and includes the replacement of the amino group by hydrogen on treatment with nitrous acid, a reaction characteristic of an amino group attached to the nitrogen of a heterocyclic ring, the formation of two different benzylidene derivatives, one of which is considered to be a Schiff base and the other a 5-methylene derivative, and a dibenzylidene derivative. The compound assigned the structure of 3-aminorhodanine, and melting at 91–92°, solidifies above the melting point and remelts at 100–101°. Sandstrom[7] attributes this behavior to polymorphism.

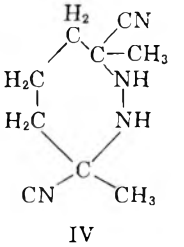
It seemed probable that evidence concerning the structure could be obtained from the infrared and ultraviolet absorption spectra of the compounds. Starting with hydrazine or substituted hydrazines and using general methods previously described, we obtained eleven compounds whose infrared and ultraviolet spectra were measured. In the synthesis, the dithiocarbazate salt was prepared from the hydrazine and carbon disulfide in the presence of a base and was treated with the salt of chloracetic acid. The cyclization was usually effected with hot hydrochloric acid. One of the compounds (IF) was prepared from 1,1-dimethylhydrazine and must necessarily have the 3-amino structure.



Overberger and Marks,[9] on the basis of infrared and chemical studies, assigned the structure of 1-amino-2,6-dicyano-2,6-dimethylpiperidine (IIIA) to the compound they had previously reported as 3,7-dicyano-3,7-dimethylhomopiperidazene (IV). They attribute a peak at 6.18–6.25 μ (1618–1600 cm.$^{-1}$) to the NH_2 bending frequency, and twin peaks in the 3 μ (3300 cm.$^{-1}$) region to NH_2 stretching. They also point out that these bands are present in 1-amino-2,6-dimethylpiperidine (IIIB). Spectral evidence was confirmed by chemical evidence.

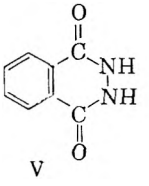


IIIa. R = CN
IIIb. R = H

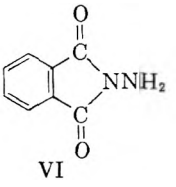


IV

A similar structure assignment, but one in which both possible isomers have been isolated and characterized by chemical evidence, is that of phthalhydrazide (V) and *N*-aminophthalimide (VI).[10] Both of these compounds were synthesized and their infrared spectra determined to discover bands which



V



VI

might be characteristic of the two structures. Bands at 3335 cm.$^{-1}$ and at 1605 cm.$^{-1}$, similar to those found by Overberger and Marks and assigned to NH stretching and NH bending, are present in the *N*-aminophthalimide spectrum but are absent from that of phthalhydrazide (see Fig. I).

A similar band at 3335 cm.$^{-1}$ and a shoulder at 1590 cm.$^{-1}$ in the cyclization product of carboxymethyl dithiocarbazate indicate that it has the structure of 3-aminorhodanine (IE) rather than that of 1,3,4-thiadiazine (IIA). Likewise, 3-anilinorhodanine (IC) and its phenyl substituted deriva-

(4) (a) R. Andreasch, *Monatsh.*, **27**, 1211 (1906); (b) R. Andreasch, *Monatsh.*, **29**, 399 (1908); (c) B. Holmberg, *J. prakt. Chem.*, [2], **81**, 451 (1910).

(5) R. A. Mathes, *J. Org. Chem.*, **17**, 877 (1952).

(6) Z. P. Sytnik, S. V. Natanson, M. V. Deichmeister, and L. D. Zhilina, *Zhur. Obshchei Khim.*, **22**, 705 (1952).

(7) J. Sandstrom, *Arkiv Kemi*, **8**, 487 (1955).

(8) H. Ueda and M. Ohta, *Nippon Kagaku Zasshi*, **77**, 385 (1956); *Chem. Abstr.*, **52**, 401 (1958).

(9) C. G. Overberger and B. S. Marks, *J. Am. Chem. Soc.*, **77**, 4097 (1955).

(10) H. D. K. Drew and H. H. Hatt, *J. Chem. Soc.*, 16 (1937).

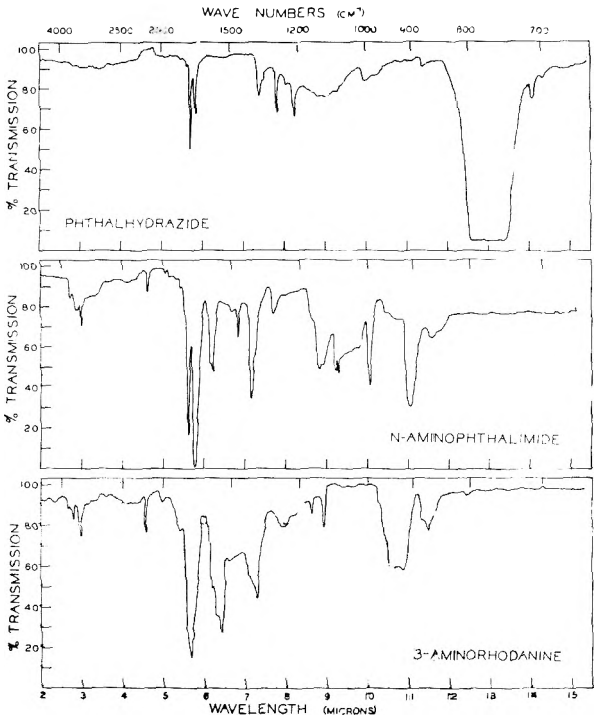


Fig. 1. Infrared absorption spectra

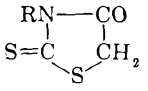
tives show bands in the same region. The absence of these bands in the spectrum of 3-dimethylaminorhodanine is further confirmation of the correctness of their assignment.

All of the compounds investigated have bands between 1745–1760 cm.$^{-1}$, which are indicative of the presence of the carbonyl group. A band between 1470–1525 cm.$^{-1}$ is within the range ascribed to the thiureide group.[11] A band in the 1250 cm.$^{-1}$ region, which is usually comparable in intensity with the carbonyl group band, is present in all the 3-aminorhodanines, while another band which is usually less intense is found between 1092–1155 cm.$^{-1}$, most frequently between 1100–1130 cm.$^{-1}$ These bands are in the general region assigned to the C=S group, but further work is necessary before either band is definitely identified with this group.[12]

Ultraviolet spectra of the 3-aminorhodanines were compared with those of rhodanine, 3-benzylrhodanine and 3-*p*-bromobenzylrhodanine. Values of λ and log ϵ are recorded in Table I. The two peaks characteristic of rhodanine, at 250.5 mμ and at 294 mμ, are present at approximately the same wave length in all cases except 3-aminorhodanine, for which the shorter wave-length peak is missing. Any shifting of wave length in the 3-anilinorhodanines is toward shorter wave length, which is opposite to what might be expected if a six-membered ring, which should be less strained than the five-membered ring, were present.[13] Values of log ϵ are of the same order of magnitude for all the compounds investigated. There is an increase in the value of log ϵ with an increase in the atomic weight of the halogen in the 3-*p*-haloanilinorhodanines.

TABLE I

ULTRAVIOLET SPECTRA OF RHODANINE DERIVATIVES



R	λ, mμ	log ϵ_{max}	λ, mμ	log ϵ_{max}
H[a]	250.5	4.12	294	4.24
$C_6H_5CH_2$	259	4.24	295	4.24
p-$BrC_6H_4CH_2$	258	4.23	295	4.24
NH_2	—	—	290.5	4.36
$(CH_3)_2N$	253.3	4.24	294.5	4.21
C_6H_5NH	250.4	4.25	287	4.23
p-FC_6H_4NH	250	4.11	289	4.17
p-ClC_6H_4NH	248	4.37	290.5	4.23
p-BrC_6H_4NH	249	4.41	290.2	4.25
p-IC_6H_4NH	245.5	4.62	288.5	4.33
p-$CH_3C_6H_4NH$	250	4.16	289	4.17
p-$CH_3OC_6H_4NH$	251	4.25	289.5	4.29
o-ClC_6H_4NH	247.5	4.08	288	4.08
2,5-$Cl_2C_6H_3NH$	246.5	4.30	290.5	4.22

[a] S. Menczel, *Z. Physik. Chem.*, **125**, 198 (1927) gives the following values for the maxima of rhodanine; λ = 250.5, log ϵ = 4.17; λ = 291.2, log ϵ = 4.32.

Table II records the results of antimicrobial testing. The compounds did not inhibit the growth of *E. coli.* and the slight inhibition of the growth of *B. subtilis* which several compounds showed does not appear to be of significant interest. However, in case of *A. niger*, the slow decrease of inhibition as the concentration was reduced seems noteworthy. Thus the four 3-*p*-haloanilinorhodanines gave a range of inhibition between 70–84% at 250 p.p.m. and between 42–54% at 10 p.p.m. With a twenty-five fold decrease in concentration the per cent inhibition decreases only 50–67% and the concentration required to inhibit 50% of the growth of the organism would be of the order of magnitude of 10 p.p.m. In their greater activity against fungi than against bacteria, the 3-anilinorhodanines resemble the previously reported 3-phenylrhodanines more closely than they do the 3-benzylrhodanines.[1]

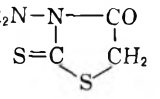
(11) H. M. Randall, R. G. Fowler, N. Fuson, and J. R. Dangl, *Infrared Determination of Organic Structures*, D. Van Nostrand Co., Inc., New York, 1949.

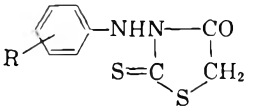
(12) Bands ascribed to C=S have been reported near 1110 cm.$^{-1}$ for thiolactams [R. Meeke and R. Meeke, *Chem. Ber.*, **89**, 343 (1956)], 1207–1225 cm.$^{-1}$ for thioketones [N. Lozać̆h and G. Guillouzo, *Bull. soc. chim. France*, 1221 (1957)], 1210–1230 cm.$^{-1}$ for thioesters [R. Felumb, *Bull. soc. chim. France*, 890 (1957)], 1346–1395 cm.$^{-1}$ for 4-substituted thiosemicarbazones and 1338–1395 cm.$^{-1}$ for 1-substituted 2-tetrazoline-5-thiones [E. Lieber, C. N. R. Rao, C. N. Pillai, J. Ramachandran, and R. D. Hites, *Can. J. Chem.*, **36**, 801 (1958)].

(13) Corresponding peaks of the less strained 2-thiono-4-keto-1,3-thiazane at 258.5 mμ (log ϵ = 4.15) and 309 mμ (log ϵ = 4.16) and of the strainfree ethyl acetyldithiocarbamate at 258.5 mμ (log ϵ = 4.16) and 309.5 mμ (log ϵ = 4.11) have been found by R. A. Potter, Ph.D. dissertation, Duke University, Durham, N. C.

TABLE II

% INHIBITION OF GROWTH OF *A. niger*





R	250 P.P.M.	200 P.P.M.	100 P.P.M.	50 P.P.M.	25 P.P.M.	10 P.P.M.	Lowest Concentration Giving Complete Inhibition of *B. subtilis*	Lowest Concentration Giving Complete Inhibition of *E. coli*
H	44%						200	>250
CH_3	30%						250	>250
H	14%						200	>250
p-F	76	72	64	60	55	50	200	>250
p-Cl	80[a]	73	64	72	68	54	200	>250
p-Br	84	68[a]	64[a]	62[a]	52[a]	42[a]	200	>250
p-I	70	64	52	46	42	42	>250	>250
p-CH_3	56	61	48				200	>250
p-CH_3O	41						200	>250
o-Cl	66	55	42				>250	>250
2,5-Cl_2	39						>250	>250

[a] Average of two separate tests.

EXPERIMENTAL

All melting points are uncorrected and were taken on a Fisher-Johns hot stage.

Hydrazines. The hydrazines used in this work were commercially available or prepared by the reduction of the corresponding diazonium salts. The hydrochlorides of *p*-chlorophenylhydrazine, *o*-chlorophenylhydrazine, and *p*-tolylhydrazine were synthesized according to the directions of Bullock and Hand.[14] *p*-Iodophenylhydrazine, melting at 95–102° (lit.[15] 103°) and *p*-methoxyphenylhydrazine, melting at 35–40° (lit.[16] 65°), were obtained by method A of the same authors in yields of 80% and 73%, respectively. *p*-Fluorophenylhydrazine hydrochloride, which melted at 208–210° after three crystallizations from hot water (lit.[17] 216°), was prepared in 64% crude yield by method B.[17] The hydrazines were usually obtained as the hydrochlorides and were neutralized with sodium hydroxide solution. If the free base was a solid at room temperature, it was isolated; if not, an ether extract of the aqueous mixture was dried and used without further treatment.

3-Aminorhodanine. This compound was prepared by the procedure of Sandstrom[7] and was obtained as yellow spears, melting at 92–93°. On tapping the glass cover plate after the first melting, crystals appeared in the drop of liquid which solidified and remelted at 102–103°. An ethanol solution of the compound could be seeded with a crystal melting at 102–103° and yielded flat crystals with the higher melting point; an ethanol solution of the higher melting crystals could be seeded with the spearlike crystals to give the lower melting form. The analytical sample was recrystallized from 95% ethanol and melted at 94.5–94.6° (lit.[7] 91–92° for needles; 100–101° for flat crystals).

Anal. Calcd. for $C_3H_4N_2OS_2$: C, 24.31; H, 2.72. Found: C, 24.37; H, 2.71.

The following derivatives, described by Sandstrom, were obtained: 3-amino-5-benzylidenerhodanine, melting at 192–195° (lit.[7] 198–200°); 3-benzylideneaminorhodanine, melting at 134–135° (lit.[7] 137–138°); 5-benzylidene-3-benzylideneaminorhodanine, melting at 168–172° (lit.[7] 172–173°); and, by treatment with nitrous acid, rhodanine, melting at 167–168°. The melting point of rhodanine was not depressed on admixture with an authentic sample.

3-Dimethylaminorhodanine. 1,1-Dimethylhydrazine (20 g.) was added to 50 ml. absolute ethanol and mixed with 50 ml. of absolute ethanol which had been saturated with ammonia. The mixture was cooled with an ice bath and stirred while 20 ml. of carbon disulfide was added dropwise. Stirring was continued 2 hr. after the addition was complete. The solid which separated was filtered, washed with a mixture of ethanol and ether, and dried giving 41 g. salt and added to an aqueous solution of sodium chloroacetate prepared by the neutralization of 25 g. chloroacetic acid with sodium carbonate. The mixture was stirred for 1 hr. and poured into 70 ml. of hot 25% hydrochloric acid. When the solution was cooled, no crystals were obtained, but the addition of 20% NaOH until the *p*H of the solution was 4 gave a white solid which was soluble in excess base. The yield of carboxymethyl 3,3-dimethyldithiocarbazate was 31 g. (61%) and after three recrystallizations from water, the analytical sample melted at 141–142.5°.

Anal. Calcd. for $C_5H_{10}N_2O_2S_2$: C, 30.91; H, 5.19; N, 14.49. Found: C, 31.19; H, 5.49; N, 14.57.

To a solution of 10 g. of the acid in 25 ml. ether and 25 ml. dioxane, 5.4 ml. of phosphorus tribromide was added carefully. The mixture was refluxed 2 hr. and poured onto ice. An oil separated which was dissolved in ethanol. After the ethanol solution had been treated with Norit, water was added to it until turbidity just appeared. The yield of 3-dimethylaminorhodanine was 3.2 g. (36%) which melted at 96–98°. After three recrystallizations the analytical sample melted at 104–104.5°.

Anal. Calcd. for $C_5H_8N_2OS_2$: C, 34.07; H, 4.57; N, 15.90. Found: C, 34.23; H, 4.65; N, 15.90.

Preparation of the 3-anilinorhodanines. One-tenth mole of the phenylhydrazine was dissolved in 150 ml. of anhydrous ether and 20 ml. of triethylamine added. The flask was sur-

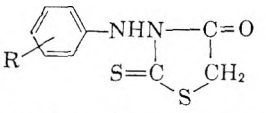
(14) M. W. Bullock and J. J. Hand, *J. Am. Chem. Soc.*, **78**, 5854 (1956).

(15) A. Neufield, *Ann.*, **248**, 93 (1888).

(16) J. Altschul, *Ber.*, **25**, 1842 (1892).

(17) I. M. Hunsberger, E. R. Shaw, J. Fugger, R. Ketcham, and D. Lednicer, *J. Org. Chem.*, **21**, 394 (1956).

TABLE III



R	M.P., °C.	Yield, %	Formula	Analyses					
				Calcd.			Found		
				C, %	H, %	N, %	C, %	H, %	N, %
H[a]	133–134[b]	38[c]	$C_9H_8N_2OS_2$						
p-F	135–137	23	$C_9H_7FN_2OS_2$	44.62	2.91	11.56	44.40	2.88	11.24
p-Cl	108.5–110.5	17.5	$C_9H_7ClN_2OS_2$[d]	41.77	2.73	10.83	41.82	2.78	10.72
p-Br	137.5–138.5	17	$C_9H_7BrN_2OS_2$	35.64	2.33	9.24	35.62	2.44	8.54
p-I	163–164.5	21	$C_9H_7IN_2OS_2$	30.87	2.01	8.00	30.87	1.84	8.19
p-CH_3	157–158	21	$C_{10}H_{10}N_2OS_2$	50.39	4.23	11.76	50.27	4.28	12.42
p-CH_3O	114.5–116	22	$C_{10}H_{10}N_2O_2S_2$	47.22	3.96	11.02	47.24	3.89	10.66
o-Cl	138.5–140	42[e]	$C_9H_7ClN_2OS_2$	41.77	2.73	10.83	41.86	2.69	10.86
2,5-Cl_2[e]	189–190[d]	6[e]	$C_9H_6Cl_2N_2OS_2$[f]	36.87	2.06		36.97	2.09	

[a] Prepared by the method of B. Holmberg, *J. prakt. Chem.*, [2] 81, 451 (1910). [b] Lit. 133.5–134° (Holmberg). [c] Crude yield. [d] Cl: Calcd., 13.70; found, 13.73. [e] This compound was obtained by treatment with PBr_3 as in the preparation of 3-dimethylaminorhodanine. [f] Cl: Calcd., 24.18; found, 24.32.

rounded by an ice bath and 10 ml. carbon disulfide added slowly while the mixture was stirred. At first an oil formed and then the solid dithiocarbazate precipitated. If necessary, seeds were obtained by dissolving a small amount of the oil in ether or ethanol and cooling or scratching the solution. Stirring was continued until the solid precipitated, which usually occurred within an hour's time. The solid was filtered, washed with ether and dried, unless evidence of decomposition (odor of hydrogen sulfide) was noticed. The solid was dissolved in 200 ml. water, using heat if necessary, and a solution of 0.1 mole sodium chloroacetate in 50 ml. water, prepared by neutralizing chloroacetic acid with sodium carbonate, was added. The mixture was stirred at room temperature until either the solid dissolved or a gum started forming in the flask or a noticeable amount of hydrogen sulfide was evolved. This required from 30 min. to 4 hr. The mixture was then poured into 100 ml. of hot 24% hydrochloric acid; heating was continued during the addition and for 20 min. afterwards or until a yellow oil or solid separated. On cooling, the product was usually a gum. If cyclization was incomplete, a white solid was present in the gum which could be removed by washing with aqueous sodium bicarbonate. The gum was washed thoroughly with water and recrystallized from absolute ethanol using Norit. Data on yields after one recrystallization (unless otherwise noted), melting points of analytical samples, and analyses are reported in Table III. The yields are not necessarily the maximum obtainable, as the purpose of this work was the preparation of small quantities of pure compounds for biological testing.

N-Aminophthalimide was prepared by the method of Drew and Hatt[10] and melted at 192–199° (lit.[10] 200–205°) after two recrystallizations from ethanol. After the first melting, needles slowly formed in the liquid drop and a second melting was observed at 338°.

Phthalhydrazide was obtained in 52% yield by heating equimolar quantities of phthalic anhydride, hydrazine sulfate, and sodium acetate in dilute acetic acid for 4 hr. After two recrystallizations from ethanol, white crystals, melting at 330–333° (lit.[10] 341–344°) were obtained.

The infrared spectra of *N*-aminophthalimide, phthalhydrazide, 3-aminorhodanine, 3-dimethylaminorhodanine, 3-anilinorhodanine, and its *p*-chloro, *p*-bromo, and 2,5-dichloro derivatives were measured in chloroform solutions using a Perkin-Elmer Model 21 spectrophotometer; the others were obtained with an Infracord using KBr plates. The ultraviolet spectra were obtained with ethanol solutions of the compounds, using a Spectracord. The antimicrobial testing procedure was identical with that previously reported.[1]

Acknowledgment. The authors are indebted to Constance M. Harris and Patricia Strickland, who assisted in the synthesis of compounds, and to Marilena Ferguson, Dorcas Clarke, Georgia Lundquist, and Priscilla Griffin, who performed the microbiological tests.

The work described in this paper was supported by a research grant [E-695(c)] from the National Institute of Allergy and Infectious Diseases, National Institutes of Health, Public Health Service.

DURHAM, N. C.

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

The Use of Substituted Phenols in the Mannich Reaction and the Dehalogenation of Aminomethylhalophenols

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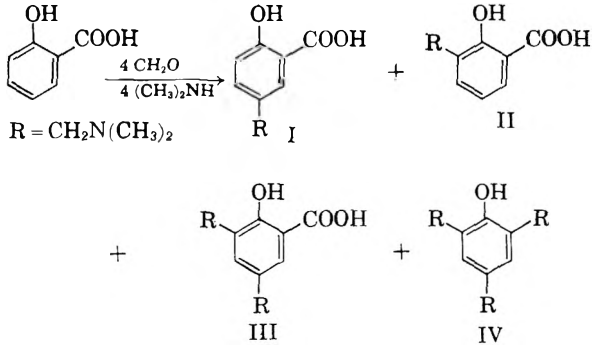
Received January 21, 1959

Twenty-two phenols which contained as substituents chlorine, bromine, hydroxyl, methyl, carboxyl, benzyloxy, benzoyloxy, or chlorohydroxybenzyl were condensed with formaldehyde and methylamine, dimethylamine, or morpholine. The aminomethylhalophenols prepared can be dehalogenated with hydrogen and platinum dioxide; in some instances, prolonged hydrogenation yielded aminomethylcyclohexanols.

A Mannich product prepared from a halophenol, during this investigation, proved to be very useful for the structure determination of a bis(aminomethyl)cyclohexanone.[3] This circumstance prompted us to make an extensive study of Mannich reactions in which a number of halophenols, as well as other types of substituted phenols, were employed. Twenty-two phenols which contained as substituents chlorine, bromine, hydroxyl, methyl, carboxyl, benzyloxy, benzoyloxy, or chlorohydroxybenzyl were condensed with formaldehyde and methylamine, dimethylamine, or morpholine. All of the aminomethyl derivatives which were prepared have been numbered and listed in Table II.

It was found that salicylic acid reacted with formalin and dimethylamine to yield a mixture of four products: 4-(dimethylaminomethyl)-2-carboxyphenol (I, 49C), 6-(dimethylaminomethyl)-2-carboxyphenol (II), 4,6-bis(dimethylaminomethyl)-2-carboxyphenol (III), and 2,4,6-tris(dimethylaminomethyl)phenol (IV). Compounds II and III were isolated as hydrochlorides (54C and 56C, respectively). The structures of I and II were



determined by hydrogenolysis with hydrogen and Raney nickel, I yielded 4-methyl-2-carboxyphenol and from II, 6-methyl-2-carboxyphenol (*o*-cresotinic acid) was obtained. The analytical data furnished proof for the structure of III. The liquid base IV is a known compound[4]; it was isolated and characterized as the trihydrochloride.

In order for IV to have been formed, one or more of the compounds—salicylic acid, I, II, or III—in the form of the dimethylamine salt or as a zwitter ion must have undergone decarboxylation during the reaction.

It was found that III, in the form of the dihydrochloride, like salicylic acid and under the same conditions, reacted with formaldehyde and dimethylamine to form a product which was isolated as the trihydrochloride and found to be identical with the trihydrochloride of IV.

Interaction of 5-chloro-2-carboxyphenol (4-chlorosalicylic acid) with formaldehyde and dimethylamine, at steam-bath temperature, produced 4-(dimethylaminomethyl)-5-chloro-2-carboxyphenol (45C) and 2,4,6-tris-(dimethylaminomethyl)-3-chlorophenol. The latter was identified in the form of its trihydrochloride by comparison with an authentic sample (43C). By removal of the chlorine atom from 45C with hydrogen and platinum dioxide, 4-(dimethylaminomethyl)-2-carboxyphenol hydrochloride was formed. The picrate of this substance was identical with the picrate of I.

When 4-chloro-2-carboxyphenol (5-chlorosalicylic acid) was allowed to react with formaldehyde and dimethylamine at 60°, 92% of the original phenol was recovered from the reaction mixture. When the reaction was carried out at steam-bath temperature, the only product which could be isolated, in 20% yield, was 2,6-bis(dimethylaminomethyl)-4-chlorophenol. This substance was found to be identical with the product (6A) obtained by the use of 4-chlorophenol in a Mannich reaction; the two compounds were compared in the form of their dihydrochlorides (7A and 8A).

4-Methyl-2-carboxyphenol reacted with formaldehyde and dimethylamine, at steam bath temperature, to yield 6-(dimethylaminomethyl)-4-methyl-2-carboxyphenol (64C) and 2,6-bis(dimethylaminomethyl)-4-methylphenol.[5] The latter compound was isolated as the dihydrochloride

(1) This paper represents part of a dissertation submitted by F. J. McCarty for the Ph.D. degree in the University of Michigan.

(2) Sterling-Winthrop Fellow.

(3) F. F. Blicke and F. J. McCarty, *J. Org. Chem.*, **24**, 1069 (1959).

(4) H. A. Bruson and C. W. MacMullen, *J. Am. Chem. Soc.*, **63**, 270 (1941).

(5) J. Décombe, *Compt. rend.*, **196**, 866 (1933).

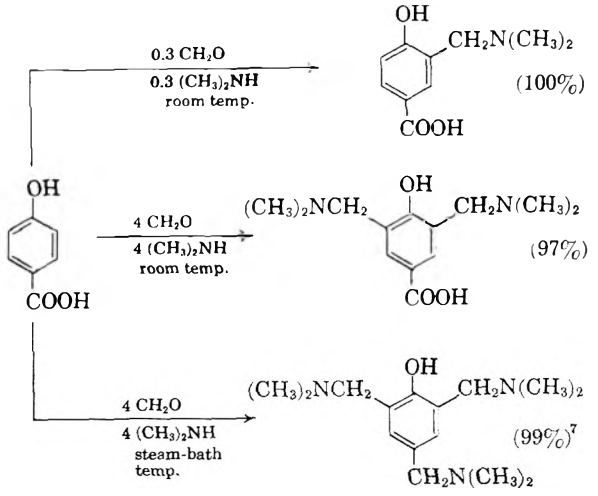
(66C). When 6-methyl-2-carboxyphenol was treated in the same manner, 4-(dimethylaminomethyl)-6-methyl-2-carboxyphenol (67C) and 2,4-bis(dimethylaminomethyl)-6-methylphenol were formed. The last mentioned phenol was identified as the dihydrochloride (69C).

From 2,4-dicarboxyphenol (4-hydroxyisophthalic acid),[6] at steam-bath temperature, 6-(dimethylaminomethyl)-2,4-dicarboxyphenol (62C) was produced.

6-(Dimethylaminomethyl)-4-bromo-5-hydroxy-2-carboxyphenol could not be synthesized from 4-bromo-5-hydroxy-2-carboxyphenol, formaldehyde and dimethylamine; the reaction product was a resin. However, it was possible to prepare the corresponding 6-(morpholinomethyl) compound (47C).

From 3-hydroxybenzoic acid, formaldehyde, and dimethylamine, 2,4,6-tris(dimethylaminomethyl)-3-carboxyphenol (57C) was obtained.

When 4-hydroxybenzoic acid was allowed to react with formaldehyde and dimethylamine at room temperature, either 2-(dimethylaminomethyl)-4-carboxyphenol (58C) or 2,6-bis(dimethylaminomethyl)-4-carboxyphenol (60C) could be isolated depending on the amounts of formaldehyde and dimethylamine employed. When the reaction was carried out at steam bath temperature, the reaction product was 2,4,6-tris(dimethylaminomethyl)phenol.



When attempts were made to introduce two dimethylaminomethyl groups into 4-benzoyloxyphenol, and three dimethylaminomethyl groups into resorcinol and into phloroglucinol, only resinous products could be isolated. However, by the use of formaldehyde and morpholine, under the same conditions, the crystalline products 2,6-bis(morpholinomethyl)-4-benzoyloxyphenol (isolated as the dihydrochloride, 74C, 50% yield), 2,4,6-tris(morpholinomethyl)-3-hydroxyphenol (70C, 100% yield) and 2,4,6-tris(morpholinomethyl)-3,5-dihydroxyphenol (78, 98% yield) were obtained.

By hydrolysis of 2,6-bis(morpholinomethyl)-4-benzoyloxyphenol dihydrochloride (74C) it was possible to obtain 2,6-bis(morpholinomethyl)-4-hydroxyphenol dihydrochloride (77C) in 91% yield. Reaction between hydroquinone, formaldehyde, and morpholine has been shown to yield 2,5-bis(morpholinomethyl)-4-hydroxyphenol.[8]

4-Benzyloxyphenol was converted into 2,6-bis(dimethylaminomethyl)-4-benzyloxyphenol dihydrochloride (73C) which, after hydrogenolysis, yielded 2,6-bis(dimethylaminomethyl)-4-hydroxyphenol dihydrochloride (76C). 2,5-Bis(dimethylaminomethyl)-4-hydroxyphenol has been obtained from hydroquinone, formaldehyde and dimethylamine.[9]

The removal of chlorine or bromine from an aminomethylhalophenol has been described by other investigators [10–12] but platinum dioxide has not been employed as a catalyst as far as we are aware.

Several halophenols were aminomethylated and the aminomethylhalophenols were dehalogenated with hydrogen and platinum dioxide. It was found that in all cases dehalogenation could be effected easily and conveniently. For example, 4,6-bis(dimethylaminomethyl)-2-chlorophenol dihydrochloride (2A) can be dehalogenated in fifteen minutes with the formation of 2,4-bis(dimethylaminomethyl)phenol dihydrochloride (5A) in 90% yield.

The halophenol employed, the aminomethylhalophenol obtained by a Mannich reaction and the aminomethylphenol prepared by dehalogenation are shown in Table I. The aminomethylhalophenols were isolated as bases and, with one exception, were used as hydrochlorides in the dehalogenation process; compound 45C was dehalogenated in the form of the base. In most instances the aminomethylphenol could be obtained as a hydrochloride. In other cases it was necessary to isolate the product as the base or picrate.

When 2-bromophenol was allowed to react with equimolar amounts of formaldehyde and dimethylamine, two mono(dimethylaminomethyl) derivatives were obtained which, in the form of their hydrochlorides, were separated by fractional recrystallization. One of the derivatives, after dehalogenation and treatment with picric acid, yielded 2-(dimethylaminomethyl)-phenol picrate, hence the

(6) This acid was obtained from the Aldrich Chemical Company.

(7) The yield is that of the trihydrochloride (35A), the

(8) W. T. Caldwell and T. R. Thompson, *J. Am. Chem. Soc.*, 61, 2354 (1939).

(9) W. T. Caldwell and T. R. Thompson, *J. Am. Chem. Soc.*, 61, 765 (1939).

(10) J. H. Burckhalter, *J. Am. Chem. Soc.*, 72, 5309 (1950).

(11) W. T. Burke and C. W. Stephens, *J. Am. Chem. Soc.*, 74, 1518 (1952).

(12) A. Cohen, R. A. Hall, B. Heath-Brown, M. W. Parkes, and A. H. Rees, *Brit. J. Pharmacol.*, 12, 194 (1957);

TABLE I

Halophenol	Aminomethylhalophenol	Aminomethylphenol
2-Chlorophenol	4,6-Bis(dimethylaminomethyl)-2-chlorophenol.2HCl (2A)	2,4-Bis(dimethylaminomethyl)-phenol.2HCl (5A)
3-Chlorophenol	2,4,6-Tris(dimethylaminomethyl)-3-chlorophenol.3HCl (43C)	2,4,6-Tris(dimethylaminomethyl)phenol.3HCl (34A)
4-Chlorophenol	2,6-Bis(dimethylaminomethyl)-4-chlorophenol.2HCl (7A)	2,6-Bis(dimethylaminomethyl)-phenol.2HCl (9A)
2,4-Dichlorophenol	6-(Methylaminomethyl)-2,4-dichlorophenol.HCl (16A)	2-(Methylaminomethyl)phenol.-HCl (17A)
2,4-Dichlorophenol	6-(Dimethylaminomethyl)-2,4-dichlorophenol.HCl (20A)	2-(Dimethylaminomethyl)phenol base (21A)
2,6-Dichlorophenol	4-(Dimethylaminomethyl)-2,6-dichlorophenol.HCl (25A)	4-(Dimethylaminomethyl)-phenol.HCl (30A)
5-Chloro-2-carboxyphenol	4-(Dimethylaminomethyl)-5-chloro-2-carboxyphenol base (45C)	4-(Dimethylaminomethyl)-2-carboxyphenol.picrate (52C)
2-(2-Hydroxy-5-chlorobenzyl)-4-chlorophenol	2-(Dimethylaminomethyl)-4-chloro-6-[3-(dimethylaminomethyl)-5-chloro-2-hydroxybenzyl]phenol.2HCl (11A)	2-(Dimethylaminomethyl)-6-[3-(dimethylaminomethyl)-2-hydroxybenzyl]phenol.2HCl (14A) 2-(Dimethylaminomethyl)-6-[3-(dimethylaminomethyl)-5-chloro-2-hydroxybenzyl]-phenol.2HCl (12A)
2-Bromophenol	4-(Dimethylaminomethyl)-2-bromophenol.HCl (27A) 6-(Dimethylaminomethyl)-2-bromophenol.HCl (26A)	4-(Dimethylaminomethyl)-phenol.picrate (31A) 2-(Dimethylaminomethyl)-phenol.picrate (23A)

original compound must have been 6-(dimethylaminomethyl)-2-bromophenol. The other derivative, after dehalogenation and treatment with picric acid, yielded 4-(dimethylaminomethyl)phenol picrate, consequently this derivative must have been 4-(dimethylaminomethyl)-2-bromophenol.

Two products, 2-(dimethylaminomethyl)-6-[3-(dimethylaminomethyl)-2-hydroxybenzyl]phenol dihydrochloride (14A) and 2-(dimethylaminomethyl)-6-[3-(dimethylaminomethyl)-5-chloro-2-hydroxybenzyl]phenol dihydrochloride (12A), were obtained when 2-(dimethylaminomethyl)-4-chloro-6-[3-(dimethylaminomethyl)-5-chloro-2-hydroxybenzyl]phenol dihydrochloride (11A) was hydrogenated by the general procedure.

When 2,4-dichlorophenol reacted with one half of a molecular equivalent of formaldehyde and the same molecular amount of methylamine, 6-(methylaminomethyl)-2,4-dichlorophenol (15A) was obtained. When the reaction was carried out with one molecular equivalent of formaldehyde and one fourth of a molecular equivalent of methylamine, the reaction product was 6-[methyl(2-hydroxy-3,5-dichlorobenzyl)aminomethyl]-2,4-dichlorophenol which was isolated as the hydrochloride (18A).

2,6-Dibromophenol, formaldehyde, and dimethylamine yielded 4-(dimethylaminomethyl)-2,6-dibromophenol (28A).

Compounds 18A and 28A were not dehalogenated.

It was found that upon prolonged hydrogenation, in the presence of platinum dioxide, 6-(dimethylaminomethyl)-2,4-dichlorophenol hydrochloride (20A) yielded 2-(dimethylaminomethyl)-cyclohexanol hydrochloride (40B). The dihydrochlorides of both 2,6-bis(dimethylaminomethyl)-4-chlorophenol (7A) and 2,6-bis(dimethylaminomethyl)phenol (9A) were converted into 2,6-bis(dimethylaminomethyl)cyclohexanol dihydrochloride; the products obtained from 7A and 9A were isolated as the dihydrochloride (38B) and base (36B), respectively. From 4-(dimethylaminomethyl)-2,6-dichlorophenol hydrochloride (25A), a mixture of the hydrochlorides of 4-(dimethylaminomethyl)cyclohexanol (41B) and dimethylaminomethylcyclohexane[13] was produced.

EXPERIMENTAL

General procedures. The molecular amounts of reactants employed in methods A–E and the structures of the products obtained by these procedures, and by methods F and G, are shown in Table II. The letter after each compound number indicates the general formula (A, B, or C) to which the compound conforms.

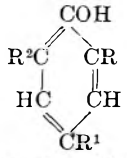
A. Formalin (37%) was added, dropwise, during a 15–30 min. period, to a stirred mixture of the required phenol and 25% aqueous dimethylamine (or morpholine or 40% aqueous methylamine) maintained at 20–25°. The mixture was stirred for 1 hr. at 25° and then for 3 hr. on a steam bath.

(13) H. Heckel and R. Adams [*J. Am. Chem. Soc.*, 47, 1712 (1925)] hydrogenated 4-dimethylaminophenol hydrochloride in the presence of platinum dioxide and sodium nitrate and obtained a mixture of 4-dimethylaminocyclohexanol, dimethylaminocyclohexane, and cyclohexane after treatment of the reaction mixture with alkali.

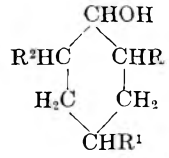
TABLE II

Aminomethyl Derivatives of Phenols and Cyclohexanol

A



(compounds 1–35, incl.)

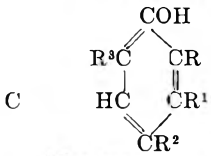


B

(compounds 36–41)

	R	R^1	R^2	Method	Molecular amounts[a]			Yield, %	M.p., °C.
1A	Cl	$CH_2N(CH_3)_2$	$CH_2N(CH_3)_2$	A	0.40	1.20	1.20	77	62–63
2A	Cl	$CH_2N(CH_3)_2$·HCl	$CH_2N(CH_3)_2$·HCl						196–197 (dec.)
3A	Cl	$CH_2N(CH_3)_2$·P[b]	$CH_2N(CH_3)_2$·P						180–181
4A	Cl	$CH_2N(CH_3)_2$·M[c]	$CH_2N(CH_3)_2$·M						113–114
5A	H	$CH_2N(CH_3)_2$·HCl	$CH_2N(CH_3)_2$·HCl	F				90	217–218
6A	$CH_2N(CH_3)_2$	Cl	$CH_2N(CH_3)_2$	A	0.40	1.20	1.20	73	103 (0.2 mm.)[d]
7A	$CH_2N(CH_3)_2$·HCl	Cl	$CH_2N(CH_3)_2$·HCl						233–234 (dec.)
8A	$CH_2N(CH_3)_2$·HCl	Cl	$CH_2N(CH_3)_2$·HCl	C	0.10	0.30	0.30	20	231–232 (dec.)
9A	$CH_2N(CH_3)_2$·HCl	H	$CH_2N(CH_3)_2$·HCl	F				77	205–206[e]
10A	[f]	Cl	$CH_2N(CH_3)_2$	A	0.10	0.40	0.40	97	140–141
11A	[f] HCl	Cl	$CH_2N(CH_3)_2$·HCl						158–160 (dec.)
12A	[f] HCl	H	$CH_2N(CH_3)_2$·HCl	F					158–160 (dec.)
13A	[g]	H	$CH_2N(CH_3)_2$						84–85
14A	[g] HCl	H	$CH_2N(CH_3)_2$·HCl	F					156–158 (dec.)
15A	$CH_2NH(CH_3)$	Cl	Cl	B	0.10	0.05	0.05	52	199–200
16A	$CH_2NH(CH_3)$·HCl	Cl	Cl						193–194 (dec.)
17A	$CH_2NH(CH_3)$·HCl	H	H	F				37	146–147[h]
18A	[i]	Cl	Cl	B	0.10	0.10	0.025	37	181–182 (dec.)
19A	$CH_2N(CH_3)_2$	Cl	Cl	A	0.40	0.80	0.80	95[j]	62–63[j]
20A	$CH_2N(CH_3)_2$·HCl	Cl	Cl						189–190[j]
21A	$CH_2N(CH_3)_2$	H	H	F				37	110–112 (10 mm.)[k]
22A	$CH_2N(CH_3)_2$·P	H	H						150–152[l]
23A	$CH_2N(CH_3)_2$·P	H	H	F[m]				42	150–152[l]
24A	Cl	$CH_2N(CH_3)_2$	Cl	A	0.06	0.12	0.12	100	184–185 (dec.)
25A	Cl	$CH_2N(CH_3)_2$·HCl	Cl						242–243 (dec.)
26A	$CH_2N(CH_3)_2$·HCl	H	Br	B	0.30	0.30	0.30	12	181–182
27A	H	$CH_2N(CH_3)_2$·HCl	Br	B	0.30	0.30	0.30	5	236–237 (dec.)
28A	Br	$CH_2N(CH_3)_2$	Br	A	0.16	0.21	0.21	89	179–180
29A	Br	$CH_2N(CH_3)_2$·HCl	Br						243–244 (dec.)
30A	H	$CH_2N(CH_3)_2$·HCl	H	F				63	184–185[n]
31A	H	$CH_2N(CH_3)_2$·P	H	F[o]				67	170–171
32A	H	$CH_2N(CH_3)_2$·P	H						170–171
33A	$CH_2N(CH_3)_2$·HCl	$CH_2N(CH_3)_2$·HCl	$CH_2N(CH_3)_2$·HCl	[p]					277–278 (dec.)
34A	$CH_2N(CH_3)_2$·HCl	$CH_2N(CH_3)_2$·HCl	$CH_2N(CH_3)_2$·HCl	F				81	275–276 (dec.)
35A	$CH_2N(CH_3)_2$·HCl	$CH_2N(CH_3)_2$·HCl	$CH_2N(CH_3)_2$·HCl	C	0.10	0.40	0.40	99	277–278 (dec.)
36B	$CH_2N(CH_3)_2$	H	$CH_2N(CH_3)_2$	G				40	80–81 (0.1 mm.)
37B	$CH_2N(CH_3)_2$·P	H	$CH_2N(CH_3)_2$·P						198–199
38B	$CH_2N(CH_3)_2$·HCl	H	$CH_2N(CH_3)_2$·HCl	G[q]				34	230–231 (dec.)

TABLE II (*Continued*)



(Compounds 42–77)

	R	R¹	R²	R³	Method	Molecular amounts[a]			Yield, %	M.p., °C.
39B	$CH_2N(CH_3)_2$	H	H		G				60	102–104 (10 mm.)[f]
40B	$CH_2N(CH_3)_2$·HCl	H	H							160–161[r]
41B	H	$CH_2N(CH_3)_2$·HCl	H		G					223–224
42C	$CH_2N(CH_3)_2$	Cl	$CH_2N(CH_3)_2$	$CH_2N(CH_3)_2$	A	0.10	0.40	0.40	92	131–132 (0.1 mm.)
43C	$CH_2N(CH_3)_2$·HCl	Cl	$CH_2N(CH_3)_2$·HCl	$CH_2N(CH_3)_2$·HCl						239–240 (dec.)
44C	$CH_2N(CH_3)_2$·HCl	Cl	$CH_2N(CH_3)_2$·HCl	$CH_2N(CH_3)_2$·HCl	C	0.10	0.40	0.40		238–239 (dec.)
45C	H	Cl	$CH_2N(CH_3)_2$	COOH	C	0.10	0.40	0.40		237–239 (dec.)
46C	H	Cl	$CH_2N(CH_3)_2$·HCl	COOH						220–221 (dec.)
47C	$CH_2NC_4H_8O$[s]	OH	Br	COOH	D	0.01	0.02	0.02	21	187–188 (dec.)
48C	$CH_2NC_4H_8O$·HCl	OH	Br	COOH						209–210 (dec.)
49C	COOH	H	$CH_2N(CH_3)_2$	H						235–240 (dec.)
50C	COOH	H	$CH_2N(CH_3)_2$·HCl	H						197–198 (dec.)
51C	COOH	H	$CH_2N(CH_3)_2$·P	H						183–184 (dec.)
52C	COOH	H	$CH_2N(CH_3)_2$·P	H	F[t]				25	183–184 (dec.)
53C	COOH	H	$CH_2N(CH_3)_2$·CH_3Br	H					33	208–209 (dec.)
54C	COOH	H	H	$CH_2N(CH_3)_2$·HCl						203–204 (dec.)
55C	COOH	H	H	$CH_2N(CH_3)_2$·P						167–168
56C	COOH	H	$CH_2N(CH_3)_2$·HCl	$CH_2N(CH_3)_2$·HCl						236–237 (dec.)
57C	$CH_2N(CH_3)_2$	COOH	$CH_2N(CH_3)_2$	$CH_2N(CH_3)_2$	C	0.10	0.50	0.50	13	177–180 (dec.)
58C	$CH_2N(CH_3)_2$	H	COOH	H	D	0.21	0.07	0.07	100	196–197 (dec.)
59C	$CH_2N(CH_3)_2$·HCl	H	COOH	H						214–215 (dec.)
60C	$CH_2N(CH_3)_2$	H	COOH	$CH_2N(CH_3)_2$	D	0.10	0.40	0.40	97	203–205 (dec.)
61C	$CH_2N(CH_3)_2$·HCl	H	COOH	$CH_2N(CH_3)_2$·HCl						219–220 (dec.)
62C	COOH	H	COOH	$CH_2N(CH_3)_2$	C	0.03	0.12	0.12	28	Above 360
63C	COOH	H	COOH	$CH_2N(CH_3)_2$·HCl						249–250 (dec.)
64C	COOH	H	CH_3	$CH_2N(CH_3)_2$	C	0.10	0.30	0.30		222–225 (dec.)
65C	COOH	H	CH_3	$CH_2N(CH_3)_2$·HCl						219–224 (dec.)
66C	$CH_2N(CH_3)_2$·HCl	H	CH_3	$CH_2N(CH_3)_2$·HCl	C	0.10	0.30	0.30		221–222[g]
67C	COOH	H	$CH_2N(CH_3)_2$	CH_3	C	0.10	0.30	0.30		224–228 (dec.)
68C	COOH	H	$CH_2N(CH_3)_2$·HCl	CH_3						209–211 (dec.)
69C	CH_3	H	$CH_2N(CH_3)_2$·HCl	$CH_2N(CH_3)_2$·HCl	C	0.10	0.30	0.30		178–179
70C	$CH_2NC_4H_8O$	OH	$CH_2NC_4H_8O$	$CH_2NC_4H_8O$	E	0.03	0.09	0.09	100	138–139
71C	$CH_2NC_4H_8O$·HCl	OH	$CH_2NC_4H_8O$·HCl	$CH_2NC_4H_8O$·HCl						179–180 (dec.)
72C	H	$CH_2N(CH_3)_2$·HCl	OH	$CH_2N(CH_3)_2$·HCl	[u]					270–271 (dec.)
73C	$CH_2N(CH_3)_2$·HCl	H	$OCH_2C_6H_5$	$CH_2N(CH_3)_2$·HCl	B	0.05	0.15	0.15	90	197–198
74C	$CH_2NC_4H_8O$·HCl	H	$OOCC_6H_5$	$CH_2NC_4H_8O$·HCl	B	0.01	0.03	0.03	50	235–236 (dec.)
75C	$CH_2N(CH_3)_2$	H	OH	$CH_2N(CH_3)_2$						129–130
76C	$CH_2N(CH_3)_2$·HCl	H	OH	$CH_2N(CH_3)_2$·HCl					85	205–206
77C	$CH_2NC_4H_8O$·HCl	H	OH	$CH_2NC_4H_8O$·HCl					91	193–194 (dec.)
78	2,4,6-Tris(morpholinomethyl)phloroglucinol				E	0.01	0.03	0.03	98	170–171
79	2,4,6-Tris(morpholinomethyl)phloroglucinol trihydrochloride									193–194 (dec.)

ANALYSES, %

		Formula	Carbon		Hydrogen		Nitrogen		Halogen	
			Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
1A	A[p]	$C_{12}H_{19}ON_2Cl$	59.36	58.83	7.89	7.85	11.54	11.40		
2A	B	$C_{12}H_{21}ON_2Cl_3$	45.64	45.77	6.71	6.93			22.47	22.15
3A	C	$C_{24}H_{25}O_{15}N_8Cl$	41.13	41.15	3.60	3.66				
4A	D	$C_{20}H_{27}O_9N_2Cl$	50.58	50.49	5.73	5.66				
5A	B	$C_{12}H_{22}ON_2Cl_2$	51.25	51.18	7.89	7.86	9.97	9.92	25.22	25.27
6A		$C_{12}H_{19}ON_2Cl$	59.30	59.08	7.89	8.04				
7A	E	$C_{12}H_{21}ON_2Cl_3$	45.64	45.84	6.71	6.86	8.88	8.66	22.47	22.53
8A	E	$C_{12}H_{21}ON_2Cl_3$					8.88	8.56		
9A	F	$C_{12}H_{22}ON_2Cl_2$	51.25	51.43	7.89	7.87	9.97	9.82	25.22	25.07
10A	G	$C_{19}H_{24}O_2N_2Cl_2$	59.54	59.51	6.31	6.48				
11A	G	$C_{19}H_{26}O_2N_2Cl_4$	50.00	49.77	5.74	6.08			15.54	15.27
12A	E	$C_{19}H_{27}O_2N_2Cl_3$	54.10	53.95	6.45	6.28				
13A	A	$C_{19}H_{26}O_2N_2$	72.59	72.52	8.34	8.34				
14A	E	$C_{19}H_{28}O_2N_2Cl_2$	58.90	58.84	7.29	7.49				
15A	G	$C_8H_9ONCl_2$	46.62	46.89	4.40	4.71	6.80	7.12		
16A	E	$C_8H_{10}ONCl_3$	39.62	39.64	4.16	4.30				
17A	H	$C_8H_{12}ONCl$	55.35	55.40	6.97	7.07			20.43	20.41
18A	H	$C_{15}H_{14}O_2NCl_5$	43.15	43.14	3.38	3.67			8.49	8.42
19A	A	$C_9H_{11}ONCl_2$	49.11	48.82	5.04	5.31				
20A	E	$C_9H_{12}ONCl_3$	42.13	42.00	4.72	4.79	5.46	5.30	13.82	13.72
24A	G	$C_9H_{11}ONCl_2$	49.11	49.11	5.04	5.06				
25A	E	$C_9H_{12}ONCl_3$	42.13	42.20	4.72	4.84	5.46	5.84	13.82	13.93
26A	E	$C_9H_{13}ONBrCl$	40.54	40.56	4.91	4.98			13.30	13.51[w]
27A	E	$C_9H_{13}ONBrCl$	40.54	40.53	4.91	4.99			13.30	13.47[w]
28A	G	$C_9H_{11}ONBr_2$	34.98	34.99	3.59	3.81			51.71	51.69
29A	G	$C_9H_{12}ONBr_2Cl$	31.29	31.34	3.50	3.45			10.27	10.30[w]
31A	F	$C_{15}H_{16}O_8N_4$	47.38	47.41	4.24	4.31				
33A	G	$C_{15}H_{30}ON_3Cl_3$	48.08	47.96	8.07	8.11			28.38	28.02
36B		$C_{12}H_{26}ON_2$	67.25	67.29	12.23	12.21				
37B	C	$C_{24}H_{32}O_{15}N_8$	42.86	42.96	4.80	5.10				
38B	E	$C_{12}H_{28}ON_2Cl_2$	50.16	50.12	9.82	9.85	9.75	9.54	24.68	24.47
41B	E	$C_9H_{20}ONCl$	55.80	55.83	10.41	10.27			18.30	18.31
42C		$C_{15}H_{26}ON_3Cl$	60.07	60.22	8.74	8.83				
43C	E	$C_{15}H_{29}ON_3Cl_4 \cdot H_2O$[x]	42.17	42.53	7.32	7.54				
45C	I	$C_{10}H_{12}O_3NCl$	52.27	52.20	5.27	5.39	6.10	6.36		
46C	E	$C_{10}H_{13}O_3NCl_2$	45.12	45.18	4.92	5.19				
47C	I	$C_{12}H_{14}O_5NBr$	43.38	43.21	4.25	4.28	4.22	4.73		
48C	E	$C_{12}H_{15}O_5NBrCl$	39.10	39.07	4.10	4.28				
49C	J	$C_{10}H_{13}O_3N$	61.53	61.39	6.71	6.68	7.18	7.27		
50C	E	$C_{10}H_{14}O_3NCl$	51.84	51.84	6.09	6.16				
51C	F	$C_{16}H_{16}O_{16}N_4$	45.29	45.38	3.80	3.81				
53C	K	$C_{11}H_{16}O_3NBr$	45.52	45.46	5.56	5.47				
54C	L	$C_{10}H_{14}O_3NCl$	51.84	51.64	6.09	6.14	6.05	6.12		
55C	F	$C_{16}H_{16}O_{16}N_4$	45.29	45.55	3.80	4.09				
56C	E	$C_{13}H_{22}O_3N_2Cl_2$	48.00	47.89	6.82	6.82	8.61	8.75		
57C	E	$C_{16}H_{27}O_3N_3$	62.11	62.27	8.80	8.85	13.58	13.72		
58C	E	$C_{10}H_{13}O_3N$	61.53	61.39	6.71	6.84	7.18	7.49		
59C	B	$C_{10}H_{14}O_3NCl$	51.84	51.63	6.09	6.29				
60C	E	$C_{13}H_{20}O_3N_2$	61.88	62.00	7.99	8.02	11.10	11.30		
61C	E	$C_{13}H_{22}O_3N_2Cl_2$	48.00	47.74	6.82	6.90				
62C	C	$C_{11}H_{13}O_5N$	55.23	54.92	5.48	5.39	5.86	5.61		
63C	E	$C_{11}H_{14}O_5NCl$	47.92	47.72	5.12	5.32				
64C	E	$C_{11}H_{15}O_3N$	63.13	63.13	7.23	7.12	6.69	6.84		
65C	E	$C_{11}H_{16}O_3NCl$	53.76	53.86	6.56	6.48				
66C	E	$C_{13}H_{24}ON_2Cl_2$	52.89	52.85	8.19	8.25			24.02	23.75
67C	E	$C_{11}H_{15}O_3N$	63.13	63.21	7.23	7.37	6.69	6.73		
68C	E	$C_{11}H_{16}O_3NCl$	53.76	53.55	6.56	6.62				
69C	H	$C_{13}H_{24}ON_2Cl_2$	52.89	52.87	8.19	8.29			24.02	23.78
70C	M	$C_{21}H_{33}O_5N_3$	61.90	62.11	8.16	8.11	10.32	10.47		
71C	E	$C_{21}H_{36}O_5N_3Cl_3$	48.79	48.59	7.02	7.18				
72C	G	$C_{12}H_{22}O_2N_2Cl_2$	48.49	48.44	7.46	7.43			23.86	23.52
73C	E	$C_{19}H_{28}O_2N_2Cl_2$	58.90	58.88	7.28	7.23			18.30	18.18
74C	N	$C_{23}H_{30}O_5N_2Cl_2$	56.91	56.71	6.23	6.34			14.61	14.42
75C	A	$C_{12}H_{20}ON_2$	64.26	63.97	8.99	8.76				
76C	E	$C_{12}H_{22}ON_2Cl_2$	48.49	48.49	7.46	7.38			23.86	23.75
77C	E	$C_{16}H_{26}O_4N_2Cl_2$	50.41	50.11	6.88	6.98			18.60	18.73
78	O	$C_{21}H_{33}O_6N_3$	59.57	59.64	7.85	7.82				
79	E	$C_{21}H_{36}O_6N_3Cl_3$	47.33	46.97	6.81	7.04			19.96	20.12

[a] Molecular amounts of reactants employed: substituted phenol, formaldehyde, and amine, respectively. [b] Picrate. [c] Maleate. [d] Boiling point. [e] J. Decombe [*Compt. rend.*, 196, 866 (1933)] described the base. [f] 2-Hydroxy-3-(dimethylaminomethyl)-5-chlorobenzyl. [g] 2-Hydroxy-3-(dimethylaminomethyl)benzyl. [h] W. J. Burke and C. W. Stephens [*J. Am. Chem. Soc.*, 74, 1518 (1952)], m.p. 144–145°. [i] $CH_2N(CH_3)CH_2C_6H_2$(OH-2)(Cl-5)—Cl-3·HCl. [j] M. Julia and G. Tchernoff [*Bull. soc. chim. France*, 830 (1955)], m.p. of base, 60°; yield 30%; m.p. of hydrochloride, 185°. [k] German patent 92,309 (*Frdl.*, 4, 103); footnote [e], b.p. 104–108° (17 mm.). [l] A. Madinaveitia [*Anales soc. espan. fis. quin.*, 19, 259 (1921); *Chem. Abstr.*, 16, 1230 (1922)], m.p. 151°. [m] Prepared by dehalogenation of 26A and treatment of the product with picric acid. [n] E. Stedman [*J. Chem. Soc.*, 1902 (1927)], m.p. 185°. [o] Prepared by dehalogenation of 27A and treatment of the product with picric acid. [p] The base of this compound was prepared as described by H. A. Bruson and C. W. Macmullen, *J. Am. Chem. Soc.*, 63, 270 (1941). [q] In this instance the product was prepared by simultaneous dehalogenation and ring hydrogenation of 7A. [r] C. Mannich and R. Braun [*Ber.*, 53, 1874 (1920)], b.p. 108° (13 mm.); m.p. of hydrochloride, 160°. [s] Morpholinomethyl. [t] Obtained in dehalogenation of 45C and treatment of the product with picric acid. [u] The base of this compound was prepared as described by W. T. Caldwell and T. R. Thompson, *J. Am. Chem. Soc.*, 61, 765 (1939). [v] Solvents used in recrystallization: A, petroleum ether (60–75°); B, isopropyl alcohol; C, water; D, acetone; E, methanol-ether; F, ethanol; G, methanol; H, isopropyl alcohol–ether; I, methanol-water; J, 90% methanol; K, ethanol-ether; L, isopropyl alcohol–ethyl acetate; M, petroleum ether (90–100°); N, isopropyl alcohol–ethyl acetate–ether; O, benzene–petroleum ether (90–100°). [w] Chlorine. [x] The water could not be removed by heating the compound at 120° (0.1 mm.) for 24 hr.

The product precipitated as a solid[14] or an oil. In the former case, it was removed by filtration. When the product separated as an oil, the mixture was treated with 160 g. of sodium chloride per mole of phenol employed. The product was extracted with ether, the extract was dried over magnesium sulfate, the solvent was removed, and the residue was distilled.

Compounds 1A and 42C could not be distilled without extensive decomposition. However, 1A crystallized after several weeks, and 42C, in crude form, was satisfactory for the preparation of the trihydrochloride (43C).

B. This procedure was the same as A except for the following variations. Ethanol[15] was used as a solvent and the addition of sodium chloride was omitted. After the heating period was completed, the mixture was concentrated *in vacuo*. The oily residue was dissolved in ether, the solution was dried and treated with hydrogen chloride. The precipitated salt was recrystallized from an appropriate solvent.

Compound 15A separated from the reaction mixture and was removed by filtration.

Compounds 26A and 27A were synthesized from 2-bromophenol. After removal of the ethanol and water *in vacuo*, the residue was distilled; b.p. 107–108° (0.1 mm.). This fraction, which consisted of a mixture of two isomeric bases, was dissolved in ether and the solution was treated with hydrogen chloride. The precipitated hydrochlorides (26A and 27A) were dissolved in methanol and ether was added until the solution became turbid. Compound 27A separated first and was recrystallized four times from methanol-ether. Compound 26A precipitated after the addition of more ether to the solution from which 27A had separated.

Compound 74C was obtained by the use of 4-benzoyloxyphenol.[16]

C. Procedure A was modified in the following manner. The addition of sodium chloride was omitted and the reaction mixture was heated under reduced pressure until all of the water had been removed. The residual oil was crystallized from ethanol or ethanol-ether.

Compound 8A. 4-Chloro-2-carboxyphenol (5-chlorosalicylic acid)[17] was used for the preparation of this product. The oily residue, obtained after removal of the water from the reaction mixture under reduced pressure, was dissolved in ether and the extract was treated with hydrogen chloride whereupon the dihydrochloride precipitated; m.p. and mixed m.p. with an authentic sample prepared by method A, 231–232° (dec.).

Compound 35A. In this instance, 4-hydroxybenzoic acid was the required phenol. The reaction mixture was heated on a steam bath for 7 hr. When the ether solution of the residual oil was treated with hydrogen chloride, the trihydrochloride precipitated; m.p. and mixed[18] m.p. 277–278° (dec.).

Compounds 44C and 45C. These compounds, in the form of a mixture, were obtained from 5-chloro-2-carboxyphenol (4-chlorosalicylic acid).[19] The residual oil was dissolved in ethanol and ether was added to the solution; 45C precipitated in crystalline form (4.6 g.). After filtration, the filtrate was treated with hydrogen chloride. The precipitated oily trihydrochloride (44C) crystallized when it was heated with isopropyl alcohol; yield 5.8 g.; m.p. 238–239° (dec.) after several recrystallizations from methanol-ether and then from methanol–ethyl acetate; mixed m.p. with an authentic sample (43C), 239–240° (dec.).

Compounds 64C and 66C. The required phenol was 4-methyl-2-carboxyphenol.[20] After the residual oil had been dissolved in ethanol and ether had been added, the precipitated crystalline product (64C) (8.0 g.) was filtered and the filtrate was treated with hydrogen chloride. After the addition of ether, the precipitated oily dihydrochloride (66C) was crystallized by heating it with isopropyl alcohol; yield 5 g.

Compounds 67C and 69C. The required phenol was 6-methyl-2-carboxyphenol (*o*-cresotinic acid).[21] The residual oil was dissolved in ethanol and ether was added to the solution. After filtration of the precipitated crystalline product (67C) (10.2 g.), the filtrate was treated with hydrogen chloride. The precipitated oil was separated, dissolved in water, the solution was made alkaline with potassium carbonate, and the oily precipitate was extracted with ether. After removal of the solvent, the product was distilled; b.p. 103–104° (0.6 mm.); yield 1.0 g. The product was converted into the dihydrochloride (69C) with ethereal hydrogen chloride.

D. After the addition of formalin, as in procedure A, the mixture was stirred for 5 hr. at room temperature, then

(14) Compounds 10A, 19A, 24A, and 28A separated as solids. 2-(2-Hydroxy-5-chlorobenzyl)-4-chlorophenol (G-4 brand of dichlorophene), required for the preparation of 10A, was obtained from the Sindar Corporation, New York, N. Y.

(15) For 15A and 18A, 50 ml. of 50% ethanol; for 26A (and 27A), 80 ml. of ethanol; for 73C, 40 ml. of ethanol, and for 74C, 25 ml. of ethanol.

(16) F. Kehrmann, M. Sandoz, and R. Monnier, *Helv. Chim. Acta*, 4, 941 (1921).

(17) Purchased from Distillation Products Industries.

(18) An authentic sample (33A) was obtained by conversion of the base, described previously (ref. 4), into the trihydrochloride.

(19) Purchased from the Aldrich Chemical Company.

(20) Obtained in 43% yield by the method of J. I. Jones [*Chem. & Ind. (London)*, 228 (1958)].

(21) Obtained from Matheson, Coleman, and Bell.

heated on a steam bath under reduced pressure until all of the water had been removed. The oily residue was crystallized from ethanol-ether.

Compound 47C. The required phenol was 4-bromo-5-hydroxy-2-carboxyphenol (5-bromo-2,4-dihydroxybenzoic acid).[6] In this instance, 25 ml. of 50% ethanol was used as a solvent. The product separated from the reaction mixture and was removed by filtration.

Compound 58C. In this case, 50 ml. of ethanol was used as a solvent. After completion of the reaction, the mixture was heated under reduced pressure until all of the water and ethanol had been removed.

E. The required phenol, morpholine, and sufficient ethanol to form a solution were shaken and treated slowly with formalin. The mixture was then allowed to remain at room temperature.

Compound 70C. After 12 hr. most of the ethanol was removed whereupon the product separated in crystalline form. The trihydrochloride (71C) melted at 212–213° (dec.) after recrystallization from methanol-ether. After it had been dried at 110° (0.1 mm.) for 12 hr., it melted at 179–180° (dec.).

Compound 78. This product precipitated after 3 hr. and was removed by filtration.

F. *Conversion of aminomethylhalophenol hydrochlorides into aminomethylphenol hydrochlorides.* A mixture of the required aminomethylhalophenol hydrochloride (0.02 mole), 75 ml. of water, and 0 2 g. of platinum dioxide was hydrogenated under an initial pressure of 55 pounds until the calculated amount of hydrogen had been absorbed (15–30 min.). After filtration, the water was removed under reduced pressure. In some instances (9A, 30A, and 34A), the oily hydrochloride crystallized when cooled. It was then recrystallized from a suitable solvent. Compound 5A was crystallized from isopropyl alcohol–ether.

Compounds 12A and 14A. These products were prepared from 11A. The mixture of oily dihydrochlorides was dissolved in methanol; upon the addition of ether, 14A precipitated in crystalline form; yield 5.5 g. After removal of 14A by filtration, ether was added to the filtrate whereupon 12A (2.0 g.) precipitated.

Compound 21A. This substance was obtained from 20A. Three hours were required for the hydrogenolysis. Since the oily hydrochloride could not be crystallized, it was converted into the base which was then distilled. The picrate was prepared from the oily hydrochloride in ethanol-water solution.

Compound 34A. This product was obtained from 43C. The reaction mixture was heated at 55–60° for 2 hr.

Compound 52C. In order to obtain this substance, 45C (the base) was hydrogenated at 55–60° for 2 hr.

Compounds 5A, 9A, 17A, 23A, 30A, 31A, and 52C were obtained from 2A, 7A, 16A, 26A, 25A, 27A, and 45C, respectively. The hydrochlorides (5A, 9A, 17A, and 30A) were isolated in crystalline form from the reaction mixtures. The picrates (23A, 31A, and 52C) were prepared by addition of picric acid, dissolved in ethanol, to an aqueous solution of the crude hydrochloride. The melting points of 23A, 31A, and 52C and the mixed melting points of each of these compounds with an authentic sample (22A, 32A, and 51C, respectively) were the same.

G. Conversion of an aminomethylphenol hydrochloride and of aminomethylchlorophenol hydrochlorides into aminomethylcyclohexanol hydrochlorides. A mixture of 0.05 mole of the required phenol hydrochloride, 200 ml. of water, and 0.5 g. of platinum dioxide was hydrogenated, at 55–60°, under an initial pressure of 55 pounds until the calculated amount of hydrogen had been absorbed. In the preparation of 39B and 41B, hydrogenation required 6 hours; the latter compound was hydrogenated at room temperature. In order to hydrogenate 7A and 9A, it was necessary to filter the mixture after 15 hr., add 0.5 g. of catalyst and hydrogenate for an additional 15 hr.

After hydrogenation had been completed, the mixture was filtered, most of the water was removed, the residue was made strongly basic, and the product was extracted with ether. The solvent was removed from the dried extract and the product was distilled.

Compound 38B. The dried extract was not distilled but was treated with hydrogen chloride. The precipitated dihydrochloride was recrystallized several times from methanol-ether.

Compound 41B. In the preparation of this substance, the desired base (1.0 g.) distilled at 120–123° (15 mm.). A lower boiling fraction was obtained and identified as dimethylaminomethylcyclohexane; yield 3.2 g.; b.p. 72–73° (15 mm.)[22]; picrate, m.p. 135–137°[22]; hydrochloride, m.p. 249–250°.

Anal. Calcd. for $C_9H_{20}NCl$: Cl, 19.94. Found: Cl, 20.10.

Compounds 36B, 38B, 39B, and 41B were prepared from 9A, 7A, 20A, and 25A, respectively.

2,4,6-Tris(dimethylaminomethyl)phenol trihydrochloride, 4-(dimethylaminomethyl)-2-carboxyphenol (49C), 6-(dimethylaminomethyl)-2-carboxyphenol hydrochloride (54C), and 4,6-bis(dimethylaminomethyl)-2-carboxyphenol dihydrochloride (56C). Salicylic acid (138 g., 1.0 mole) and 25% aqueous dimethylamine (720 g., 4.0 moles) were stirred and maintained at 20–25° while 37% formalin (324 g., 4.0 moles) was added, dropwise, during a 30-min. period. The mixture was stirred for 1 hr. and then stirred and heated for 3 hr. on a steam bath. The oily residue obtained, after removal of the water under reduced pressure, was dissolved in 500 ml. of hot ethanol. When the solution was cooled, 48 g. of 49C precipitated and was removed by filtration. The filtrate was treated with hydrogen chloride and the precipitated 2,4,6-tris(dimethylaminomethyl)phenol trihydrochloride (47 g.) was filtered; m.p. and mixed[18] m.p. 277–278° (dec.). The filtrate was treated with ether until it became turbid. The mixture was cooled and the precipitate, 61 g. of 56C, was removed by filtration. After the solvents had been removed from the filtrate, the oily residue was dissolved in hot isopropyl alcohol and ethyl acetate was added until the solution became cloudy. After 4 weeks, 15 g. of 54C precipitated.

A sample of 49C, dissolved in absolute ethanol, was heated with excess methyl bromide at 65° for 24 hr. After ether had been added, the methobromide (53C) precipitated.

Preparation of salts. The hydrochlorides, 2A, 7A, 11A, 16A, 20A, 33A, 40B, 41B, 43C, 71C, and 79, precipitated when a solution of the base in ether was treated with hydrogen chloride. In the case of 25A and 29A, absolute methanol was used as the solvent.

Compounds 46C, 48C, 50C, 59C, 61C, 63C, 65C, and 68C precipitated upon the addition of ether to a methanol solution of the base which had been treated with hydrogen chloride. Compound 72C was obtained in the same manner except that ethanol was used as a solvent.

The dipicrate 37B was obtained by addition of picric acid, dissolved in ethanol, to a solution of the base, 36B, in the same solvent. The dipicrate 3A was obtained in the same manner from the dihydrochloride 2A. The picrates 22A, 32A, and 55C were prepared from the oily hydrochloride of 21A and the hydrochlorides 30A and 54C, respectively, by the addition of an ethanol solution of picric acid to a solution of the hydrochloride in water. Compound 51C was prepared by the same process except that an aqueous solution of the base, 49C, was used.

The dimaleate 4A was obtained by mixing methanol solutions of the base, 1A, and maleic acid and then adding ether to precipitate the salt.

Structure proof of 4-(dimethylaminomethyl)-2-carboxyphenol hydrochloride (50C). A solution of 1.5 g. of 50C in 20 ml. of water, which had been made alkaline with potassium car-

(22) M. Mousseron, R. Jacquier, and R. Zagdoun [*Bull. soc. chim. France*, 197 (1952)], b.p. 75–76° (15 mm.); picrate, m.p. 133°.

bonate, was added to 2 g. of wet Raney nickel paste[23] and the mixture was hydrogenated at 55–60° under an initial pressure of 52 pounds until the calculated amount of hydrogen had been absorbed (20 hr.). After removal of the catalyst by filtration, the cooled filtrate was acidified with concentrated hydrochloric acid. The precipitated 4-methyl-2-carboxyphenol weighed 0.75 g. (76%); m.p. 152–153°.

Structure proof of 6-(dimethylaminomethyl)-2-carboxyphenol hydrochloride (54C). This procedure, with the use of 54C, was carried out in the manner mentioned above. The product, 6-methyl-2-carboxyphenol, weighed 0.3 g. (30%); m.p. 165–166°; reported[24] m.p. 167°; mixed m.p. with an authentic sample, 165–166°.

Reaction of 4,6-bis(dimethylaminomethyl)-2-carboxyphenol dihydrochloride (56C) with formaldehyde and dimethylamine. A mixture of 3.3 g. (0.01 mole) of 56C, 5.0 g. (0.06 mole) of formalin and 11.0 g. (0.06 mole) of 25% aqueous dimethylamine was heated on a steam bath for 3 hr. The mixture was made alkaline with potassium carbonate and then concentrated until most of the water had been removed. The residue was extracted with ether and the dried extract was treated with hydrogen chloride. The precipitated 2,4,6-tris(dimethylaminomethyl)phenol trihydrochloride (0.5 g.) was recrystallized from methanol; m.p. 276–277° (dec.); mixed m.p. with an authentic sample (33A), 276–277° (dec.).

2,6-Bis(dimethylaminomethyl)-4-hydroxyphenol dihydrochloride (76C). A mixture of 3.9 g. of 2,6-bis(dimethylaminomethyl)-4-benzyloxyphenol dihydrochloride (73C), 50 ml. of acetic acid and 2.5 g. of palladium on carbon[25] was hydrogenated under an initial pressure of 14 pounds for 15 min. The mixture was filtered and the solvent was removed under reduced pressure. The oily residue was crystallized from hot isopropyl alcohol; yield 2.5 g. (85%); m.p. 205–206° (dec.) after recrystallization from methanol-ether.

2,6-Bis(morpholinomethyl)-4-hydroxyphenol dihydrochloride (77C). A solution of 2.0 g. of 2,6-bis(morpholinomethyl)-4-benzoyloxyphenol dihydrochloride (74C) in 30 ml. of 18% hydrochloric acid was heated for 3 hr. on a steam bath. The mixture was cooled and filtered to remove benzoic acid (0.45 g.). The water and hydrochloric acid were removed under reduced pressure and the residue was recrystallized from methanol-ether; yield 1.4 g. (91%); m.p. 115–116° (dec.). After the product had been dried at 65° (0.1 mm.) for 24 hr., it melted at 193–194° (dec.).

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(23) Sponge Nickel Catalyst which was obtained from the Davison Chemical Company, Division of W. R. Grace and Company, Department T, Baltimore 3, Md.

(24) N. V. Sidgwick, *J. Chem. Soc.*, **117**, 396 (1920).

(25) Obtained from Baker and Company, Newark, N. J.

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

Disubstitution of Cycloalkanones in the Mannich Reaction

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Received January 21, 1959

Ten bis(aminomethyl)cycloalkanones were prepared by the simultaneous introduction of two aminomethyl groups into a cycloalkanone by the use of a Mannich reaction. It was definitely established that the reaction product obtained from cyclohexanone, paraformaldehyde and dimethylamine hydrochloride was 2,6-bis(dimethylaminomethyl)cyclohexanone dihydrochloride and not the salt of the isomeric 2,2-disubstitution product.

The introduction of one aminomethyl group into a ketone by the use of a Mannich reaction has been reported in many instances but only a relatively few examples are known in which two aminomethyl groups have been introduced into a ketone either intentionally or fortuitously.

It was reported that acetone reacts with formaldehyde and dimethylamine[3,4] or diethylamine,[4,5] under certain conditions, with the formation of a 1,1-bis(dialkylaminomethyl)acetone, and the structures of these products have been definitely established.

From acetone, formaldehyde, and hexahydroazepine hydrochloride the disubstituted acetone 2-acetylpropane-1,3-bis(hexahydro-1-azepine) dihydrochloride has been obtained.[6]

1,1,1-Trifluoroacetone reacted with the methylols of piperidine, morpholine, and diisobutylamine to form products which appeared to be hydrates of the bis(aminomethyl)ketone.[7]

A disubstitution product obtained from methyl ethyl ketone, formaldehyde, and dimethylamine hydrochloride has been stated to be either 1-dimethylamino-4-(dimethylaminomethyl)-3-pentanone or 3,3-bis(dimethylaminomethyl)-2-butanone by Cardwell[4] but according to Barrett and Chambers[8] the product is the former compound; Haeussler and Schacht[9] claim that the product is the latter substance.

From propiophenone and from 3-acetylpyridine, β,β'-bis(1-piperidyl)pivalophenone and bis(1-piperidylmethyl)methyl-3-pyridyl ketone, respectively, were obtained by Mannich reactions.[10]

(1) This paper represents part of a dissertation submitted by F. J. McCarty for the Ph.D. degree in the University of Michigan.

(2) Sterling-Winthrop Fellow.

(3) C. Mannich and O. Salzmann, *Ber.*, **72**, 506 (1939).

(4) H. M. E. Cardwell, *J. Chem Soc.*, 1056 (1950).

(5) A. L. Wilds and C. H. Shunk, *J. Am. Chem. Soc.*, **65**, 469 (1943).

(6) R. P. Mull, P. Schmidt, M. R. Dapero, J. Higgins, and M. J. Weisbach, *J. Am. Chem. Soc.*, **80**, 3769 (1958).

(7) G. F. Grillot, S. Aftergut, S. Marmor, and F. Carrock, *J. Org. Chem.*, **23**, 386 (1958).

(8) P. A. Barrett and K. A. Chambers, *J. Chem. Soc.*, 338 (1958).

(9) H. Haeussler and W. Schacht, *Chem. Ber.*, **83**, 129 (1950).

(10) J. J. Denton, R. J. Turner, W. B. Neier, V. A. Lawson, and H. P. Schedl, *J. Am. Chem. Soc.*, **71**, 2048 (1949).

The object of this investigation was the discovery of a satisfactory method for the preparation of bis-(aminomethyl)cycloalkanones by the use of the Mannich reaction.

It had been reported[11] that the interaction of cyclopentanone, formaldehyde, and morpholine hydrochloride yielded 2,5-bis(morpholinomethyl)-cyclopentanone dihydrochloride but the structure of the product was not proven.

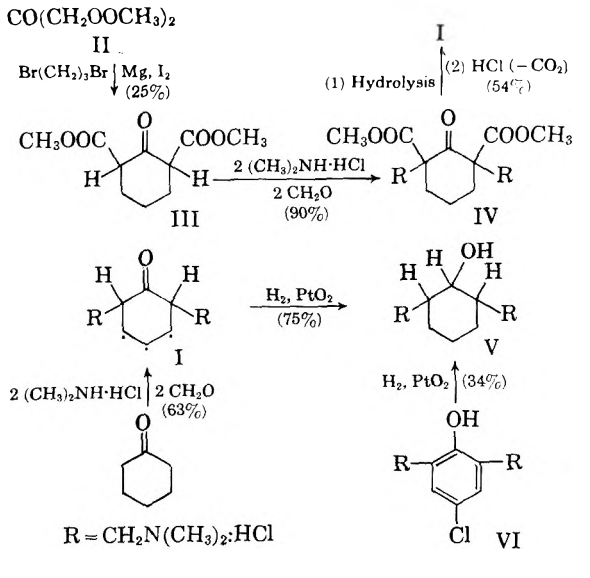
Compounds which were described[8] as 2,5-bis-(dimethylaminomethyl)cyclopentanone, 2,6-bis-(dimethylaminomethyl)cyclohexanone,[12] and 2,7-bis(dimethylaminomethyl)cycloheptanone have been obtained by the Mannich reaction but it was stated that "The possibility that the bis(dimethylaminomethyl)cycloalkanones are α,α-disubstituted cycloalkanones has not been rigorously disproved."

In a brief report, in which experimental procedures were not mentioned, Mühlstädt[12a] stated that he had obtained the dihydrochlorides of bis-(piperidinomethyl)cyclopentanone, bis(dimethylaminomethyl)- and bis(piperidinomethyl)cyclohexanone, bis(dimethylaminomethyl)- and bis-(piperidinomethyl)cycloheptanone. The structures of these compounds were proven by pyrolysis of the hydrochlorides of the bis(piperidinomethyl)-derivatives; the dimethylenecycloalkanones obtained were converted by hydrogenation into α,α'-dimethylcycloalkanones. This investigator reported melting points for the dihydrochlorides of the bis(dimethylaminomethyl) derivatives of cyclohexanone and cycloheptanone which are 15–25° lower than those found by Barrett and Chambers and by us.

We have found that, under proper conditions, cyclopentanone, cyclohexanone, cycloheptanone,[13] and cyclooctanone[14] will react with paraformaldehyde and a secondary amine hydrochloride in acetic acid to form salts of the bis(aminomethyl)-cycloalkanone type in 22–90% yields (Table I). In the case of the disubstitution product obtained from cyclohexanone, paraformaldehyde, and dimethylamine hydrochloride, it was proven by the two processes described below that the compound was 2,6 - bis(dimethylaminomethyl)cyclohexanone dihydrochloride (I) and not the salt of the isomeric 2,2-disubstitution product.

Diethyl acetonedicarboxylate had been shown[15] to react with 1,3-dibromopropane and magnesium to form diethyl cyclohexanone-2,6-dicarboxylate the structure of which was proven by its transformation into cyclohexanone by hydrolysis and decarboxylation.

We converted the commercially available dimethyl acetonedicarboxylate (II) into dimethyl cyclohexanone-2,6-dicarboxylate (III) and by the use of a Mannich reaction obtained dimethyl 2,6 - bis(dimethylaminomethyl)cyclohexanone - 2,6-dicarboxylate dihydrochloride (IV) from III. Samples of III and IV were converted into the corresponding secondary alcohols. After hydrolysis and decarboxylation of IV, a product was obtained which, in the form of its dihydrochloride, was identical with the product (I) prepared from cyclohexanone, paraformaldehyde and dimethylamine hydrochloride. Furthermore, two samples of the oxime dihydrochloride, one obtained from I which had been prepared by the use of cyclohexanone, the other from I which had been prepared by hydrolysis and decarboxylation of IV, proved to be identical. Consequently, compound I must be 2,6-bis(dimethylaminomethyl)cyclohexanone dihydrochloride.



In order to obtain further proof of the structure of I, this compound was reduced to the corresponding secondary alcohol (V). Compound V proved to be identical with the secondary alcohol which had been obtained previously[16] by simultaneous dehalogenation and ring hydrogenation of 2,6-bis-(dimethylaminomethyl)-4-chlorophenol dihydrochloride (VI). The structure of the last mentioned compound was established by its synthesis from 4-chlorophenol, formaldehyde, and dimethylamine.[16]

(11) R. H. Harradence and F. Lions, *J. Proc. Roy. Soc. N. S. Wales*, **72**, 233 (1938).

(12) It was stated by E. Jeney and T. Zsolnai [*Acta Microbiol. Acad. Sci. Hung.*, **2**, 249 (1955)] that 2,6-bis-(diethylaminomethyl)cyclohexanone was tested for its effect on Brucella abortus. Neither the method of preparation nor the physical properties of the product were mentioned in the abstract.

(12a) M. Mühlstädt, *Naturwissenschaften*, **45**, 240 (1958); *Chem. Abstr.*, **53**, 4274 (1959).

(13) F. F. Blicke, N. J. Doorenbos, and R. H. Cox, *J. Am. Chem. Soc.*, **74**, 2924 (1952).

(14) F. F. Blicke, J. Azuara, N. J. Doorenbos, and E. B. Hotelling, *J. Am. Chem. Soc.*, **75**, 5418 (1953).

(15) P. C. Guha and N. K. Seshadriengar, *Ber.*, **69**, 1207 (1936).

(16) F. F. Blicke and F. J. McCarty, *J. Org. Chem.*, **24**, 1061 (1959).

The benzilate was prepared from the secondary alcohol (V), obtained from I, and from the secondary alcohol (V) prepared from VI; the two benzilates proved to be identical.

The diphenylacetyl and diphenylchloroacetyl derivatives of V were also synthesized.

The introduction of two aminomethyl groups into cyclohexanone unquestionably takes place in the 2 and 6 positions. Although this fact does not necessitate the assumption that disubstitution takes place in the same manner in the case of smaller or larger cycloalkanones, the disubstituted cycloalkanones listed in Table I have been described, arbitrarily, as compounds in which the introduced aminomethyl groups occupy positions which correspond to the 2,6 positions in cyclohexanone.

The highest yield of I (63%) was obtained by the use of the general procedure in which the cyclic ketone, paraformaldehyde, and the amine hydrochloride were heated in acetic acid solution at 95° for two and one-half hours. When changes were made in this process such as the use of absolute ethanol as a solvent instead of acetic acid, the use of more than two molecular equivalents of paraformaldehyde and dimethylamine hydrochloride, heating the reaction mixture for a longer time or at a higher or lower temperature, compound I was formed in lower yield. In a separate experiment, it was shown that I does not undergo even partial decomposition under the conditions employed in the general procedure.

2,6-Bis(diethylaminomethyl)- and 2,6-bis(dibenzylaminomethyl)cyclohexanone dihydrochloride could be obtained by the general procedure only when the reaction temperature was maintained below 80°. It was found that after the latter compound had been heated in acetic acid for two and one-half hours at 95°, dibenzylamine hydrochloride could be isolated in 88% yield. 2-(Dibenzylaminomethyl) cyclohexanone hydrochloride was prepared (reaction temperature 55–60°) and it was found that this substance also underwent decomposition when treated in the manner described above; dibenzylamine hydrochloride was obtained in 90% yield.

Although 2,6-bis(methylbenzylaminomethyl)-cyclohexanone dihydrochloride could be prepared by the general procedure (95°), we found that the monosubstitution product, 2-(methylbenzylaminomethyl)cyclohexanone hydrochloride could be obtained in pure form only when the reaction mixture was maintained at 75–80°.

2,6 - Bis(methylbenzylaminomethyl)cyclohexanone dihydrochloride and 2-(methylbenzylaminomethyl)cyclohexanone hydrochloride can be debenzylated by the use of hydrogen and palladium on carbon to the corresponding bis(methylaminomethyl) and the methylaminomethyl compounds, respectively. There was no reduction of the carbonyl group in these instances since both of the compounds exhibited the characteristic carbonyl infrared absorption band at 1690 cm.$^{-1}$ [17]; furthermore, an oxime was obtained from the methylaminomethyl compound.

2-(Dimethylaminomethyl)cyclohexanone hydrochloride reacted with paraformaldehyde and dimethylamine hydrochloride to form 2,6-bis(dimethylaminomethyl)cyclohexanone dihydrochloride (I) and with paraformaldehyde and piperidine hydrochloride to yield 2-(dimethylaminomethyl)-6-(piperidinomethyl)cyclohexanone dihydrochloride.

Compound I reacted with phenylmagnesium bromide and also with phenyllithium to form 2,6-bis(dimethylaminomethyl) - 1 - phenylcyclohexanol, and with 2-pyridyllithium to form 2,6-bis(dimethylaminomethyl)-1-(2-pyridyl)cyclohexanol.[8] These alcohols were converted into the corresponding propionates by the use of propionic anhydride.

The oxime of I was reduced with lithium aluminum hydride to 2,6-bis(dimethylaminomethyl)-1-aminocyclohexane.

The secondary alcohol was obtained from 2,5-bis(dimethylaminomethyl)cyclopentanone dihydrochloride by the use of sodium borohydride.

When compound IV was hydrogenated catalytically in acetic acid solution, the corresponding carbinol was obtained in 46% yield. The process was repeated with methanol as the solvent. In this instance the yield of carbinol was only 12%, and from the reaction mixture there was also isolated dimethyl cyclohexanone-2,6-dicarboxylate and trimethylamine hydrochloride. It is assumed that these last two products were obtained by a Mannich reversal reaction in which the ester and dimethylhydroxymethylamine hydrochloride may have been formed; hydrogenation of the latter would account for the formation of the trimethylamine salt. It seems probable that the reaction mixture may also have contained dimethyl cyclohexanol-2,6-dicarboxylate since, in a separate experiment, it was shown that under the conditions used in the reaction dimethyl cyclohexanone-2,6-dicarboxylate can be reduced to the corresponding alcohol.

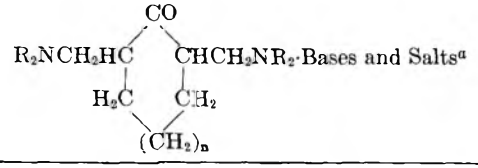
In order to determine the extent to which IV would undergo a reversal reaction under more favorable conditions, IV has heated in aqueous solution for 3.5 hours on a steam bath.[18] The products obtained from the reaction mixture were

(17) It has been shown by R. Simonoff and W. H. Hartung (*J. Am. Pharm. Assoc. Sci. Ed.*, **35**, 306 (1946)) that in the debenzylation of α-benzylamino and α-dibenzylamino ketones with palladium on carbon either the α-amino ketone or the corresponding secondary alcohol can be obtained.

(18) An instance of the reversal of a Mannich product under similar conditions was reported by W. E. Bachmann and L. B. Wick [*J. Am. Chem. Soc.*, **72**, 3388 (1950)].

TABLE 1

BIS(AMINOMETHYL)CYCLOALKANONE BASES AND SALTS



·Bases and Salts[a]

	n	NR_2	Yield, %	M.p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Halogen Calcd.	Halogen Found
1	0	$N(CH_3)_2$	32	187–188[b]	$C_{11}H_{24}ON_2Cl_2$	48.71	48.80	8.92	8.86	10.33	10.08	26.15	25.89
2	0	$N(CH_3)_2$	31	198–199	$C_{11}H_{24}ON_2Br_2$	36.67	36.91	6.71	6.57	7.78	7.86	44.38	43.95
3	0	C_4H_8ON[c]	69	202–203[d]	$C_{15}H_{28}O_3N_2Cl_2$					7.89	7.95	19.96	19.85
4	1	$NHCH_3$[e]	42	167–168	$C_{10}H_{22}ON_2Cl_2$	46.70	46.44	8.63	8.71	10.90	10.60	27.58	27.15
5	1	$N(CH_3)_2$	63	177–178[f]	$C_{12}H_{26}ON_2Cl_2$	50.51	50.55	9.19	9.17	9.82	10.12	24.85	24.56
6	1	$N(CH_3)_2$		80–81[g,h] (0.05 mm.)	$C_{12}H_{24}ON_2$	67.89	68.22	11.40	11.52				
7	1	$N(CH_3)_2$	8	188–189	$C_{12}H_{26}ON_2Br_2$	38.51	38.64	7.01	7.04	7.49	7.30	42.72	42.36
8	1	$N(C_2H_5)_2$		137–138	$C_{28}H_{38}O_{15}N_8$	46.29	46.32	5.27	5.28				
9	1	$N(C_2H_5)_2$	22	110–111[h] (0.2 mm.)	$C_{16}H_{32}ON_2$	71.59	71.52	12.02	11.80	10.44	9.85		
10	1	C_4H_8ON	57	163–164	$C_{16}H_{30}O_3N_2Cl_2$	52.04	51.63	8.19	8.17	7.59	7.66	19.20	18.80
11	1	$C_5H_{10}N$[i]		162–163	$C_{30}H_{38}O_{16}N_8$	48.00	48.08	5.10	5.20				
12	1	$C_5H_{10}N$	34	83–84[j]	$C_{18}H_{32}ON_2$	73.94	74.22	11.03	10.89				
13	1	$N(CH_3)CH_2C_6H_5$	55	169–170	$C_{24}H_{34}ON_2Cl_2$	65.89	65.79	7.83	7.99	6.40	6.43	16.21	15.97
14	1	$N(CH_2C_6H_5)_2$	90	249–250[k]	$C_{36}H_{42}ON_2Cl_2$	73.34	73.14	7.18	7.28			12.03	12.03
15	1	$N(CH_2C_6H_5)_2$		108–109[j]	$C_{36}H_{40}ON_2$	83.70	83.58	7.80	7.91	5.42	5.62		
16	2	$N(CH_3)_2$	42	168–169[l]	$C_{13}H_{28}ON_2Cl_2$	52.17	52.16	9.43	9.45	9.36	9.51	23.69	23.47
17	3	$N(CH_3)_2$	43	179–180	$C_{14}H_{30}ON_2Cl_2$	53.68	53.47	9.65	9.64	8.95	8.85	22.63	22.16

[a] Dihydrochloride, dihydrobromide, or dipicrate. [b] Ref. 8, m.p. 185–186°. [c] Morpholino. [d] Ref. 11, m.p. 195°. [e] Obtained by debenzylation of compound 13. [f] Ref. 8, m.p. 169–170°. Ref. 12a, m.p. 152–153°. [g] Ref. 8, b.p. 90–94° (0.4 mm.). [h] B.p. of base. [i] Piperidino. [j] M.p. of base. [k] Softened at 160°. [l] Ref. 8, m.p. 170–171°. Ref. 12a, m.p. 153–156°.

Compounds 1, 2 and 3 were recrystallized from methanol; 4 from isopropyl alcohol; 5, 7, 13, 14, 16, and 17 from methanol-ether; 8, 10, 11, and 15 from ethanol; 12 from petroleum ether (60–75°).

dimethyl cyclohexanone-2,6-dicarboxylate (47%), formaldehyde and dimethylamine hydrochloride.[19]

EXPERIMENTAL

Bis(aminomethyl)cycloalkanone dihydrochlorides. General procedure. (Table I, compounds 1, 5, 10, 13, 16, and 17). A mixture of 0.1 mole of the cycloalkanone, 0.2 mole of paraformaldehyde, 0.2 mole of the amine hydrochloride, and 40 ml. of acetic acid was maintained at 95° for 2.5 hr. The mixture was shaken occasionally until a solution was obtained. The solvent was removed on a steam bath under reduced pressure. The oily residue[20] was dissolved in 70 ml. of hot acetone, the solution was cooled and the precipitated dihydrochloride was recrystallized.

Instances in which compounds reported in Table I were prepared by a variation of the general procedure or by a different process are mentioned below.

Compound 12. Since the crystalline dihydrochloride could not be purified by recrystallization, it was converted into the solid base which was then purified by recrystallization from petroleum ether (60–75°). The dipicrate (11) was prepared in ethanol.

Compound 9. The reaction temperature was maintained at 75–80°, and after removal of the solvent, the residue was made alkaline and the oily product was distilled. The first fraction (9.0 g.), which boiled at 73–80° (0.4 mm.),[21] proved to be 2-(diethylaminomethyl)cyclohexanone. The picrate melted at 118–119° after recrystallization from water.

Anal. Calcd. for $C_{17}H_{24}O_8N_4$: C, 49.51; H, 5.87. Found: C, 49.50; H, 5.92.

The second fraction (6.0 g.), b.p. 110–111° (0.2 mm.), was found to be compound 9. Since the dihydro hloride was found to be very hygroscopic, a sample of the base was dissolved in ethanol and the solution was treated with picric acid whereupon the dipicrate (8) precipitated.

Compound 14. This product was prepared by the general procedure but it was necessary to maintain the temperature at 55–60°, and 160 ml. of acetic acid was employed as solvent. A portion of the dihydrochloride was converted into the base (15).

The unfavorable effect of a higher temperature in the preparation of 14 was shown by the following experiment. A mixture of 2.0 g. of 14 and 10 ml. of acetic acid was heated at 95° for 2.5 hr. and the solvent was then removed. The solid residue, after it had been purified by boiling it with acetone, was found to be dibenzylamine hydrochloride; yield 1.4 g. (88%); m.p. and mixed m.p. 257° (dec.).

Compound 2. A mixture of 8.4 g. (0.1 mole) of cyclopentanone, 31.5 g. (0.25 mole) of dimethylamine hydrobromide, 9.0 g. (0.3 mole) of paraformaldehyde and 50 ml. of absolute ethanol was refluxed for 24 hr. The precipitated product (11.0 g., 31%, m.p. 196–199°) was recrystallized from methanol.

Compound 3. This compound was synthesized in the same general manner as 2 except that 0.25 mole of morpholine hydrochloride was used and the reaction mixture was refluxed for 17 hr.; the precipitated, crude product (24.0 g.) melted at 193–194° and at 202–203° after recrystallization from methanol.

Compound 7. This compound was prepared in the same general manner as 2 except that 0.1 mole of cyclohexanone was employed. Since the product did not precipitate from the reaction mixture, the solvent was removed under reduced pressure. The oily residue became crystalline when it was triturated with isopropyl alcohol; yield 7.0 g. After several recrystallizations from methanol-ether, 2.8 g. of pure product was obtained.

Effect of solvent. The very marked difference in the yield of compound I obtained by the use of acetic acid or ethanol as a solvent is shown by the following experiments.

(a) A mixture of 98.1 g. (1 mole) of cyclohexanone, 60.0 g. (2 moles) of paraformaldehyde, 163.1 g. (2 moles) of dimethylamine hydrochloride, and 400 ml. of acetic acid was heated at 95° for 2.5 hr. The solvent was removed under reduced pressure and the solid residue was refluxed for a short time with 500 ml. of acetone. The undissolved dihydrochloride (I) was filtered; yield 175.0 g. (62%); m.p. 177–178°. Upon removal of the acetone from the filtrate, treatment of the residue with alkali and distillation, 8.5 g. of 2-(dimethylaminomethyl)cyclohexanone was obtained; b.p. 100–103° (20 mm.).[22] The hydrochloride melted at 155°.[22]

(b) The experiment described above was repeated but in place of acetic acid, 400 ml. of absolute ethanol was used. After removal of the solvent under reduced pressure, the residue was treated with alkali and then distilled. There was obtained 23.0 g. of 2-(dimethylaminomethyl)cyclohexanone, b.p. 70–75° (0.4 mm.) (the hydrochloride melted at 155–156°) and 13.5 g. (6%) of the base of I which boiled at 93–97° (0.4 mm.)[23] (compound 6) (the dihydrochloride melted at 176–177°). An analytical sample of 6 boiled at 80–81° (0.05 mm.).

In an attempt to determine whether or not the yield of the disubstitution product would be increased by the use of amounts of paraformaldehyde and dimethylamine hydrochloride greater than two molecular equivalents, a mixture of 4.9 g. (0.05 mole) of cyclohexanone, 9.0 g. (0.3 mole) of paraformaldehyde, 20.5 g. (0.25 mole) of dimethylamine hydrochloride and 20 ml. of acetic acid was heated at 95° for 2.5 hr. After removal of the solvent, treatment of the residue with alkali and distillation, only 2.8 g. (8%) of the base of I (6) was obtained.

In order to determine whether or not compound I underwent partial decomposition during its preparation by the general procedure, a solution of 28.5 g. of this substance (m.p. 178–179°) in 40 ml. of acetic acid was heated at 95° for 2.5 hr., the solvent was removed under reduced pressure and the material was purified by boiling it with acetone. The recovered salt weighed 27.8 g.; m.p. 179–180°.

2-(Dibenzylaminomethyl)cyclohexanone hydrochloride. A mixture of 9.8 g. (0.1 mole) of cyclohexanone, 1.5 g. (0.05 mole) of paraformaldehyde, 11.7 g. (0.05 mole) of dibenzylamine hydrochloride, and 50 ml. of acetic acid was heated for 2.5 hr. at 55–65°. The solvent was removed under reduced pressure at a temperature below 65°. The oily residue was dissolved in hot acetone. The crystalline product which separated from the cold solution softened at 170° and melted at 239–240° (dec.); yield 16.3 g. (95%).

Anal. Calcd. for $C_{21}H_{26}ONCl$: C, 73.35; H, 7.62; Cl, 10.31. Found: C, 73.24; H, 7.48; Cl, 10.62.

The picrate, prepared from the hydrochloride in ethanol, melted at 159–160° after recrystallization from ethanol.

Anal. Calcd. for $C_{27}H_{28}O_8N_4$: C, 60.43; H, 5.26. Found: C, 60.48; H, 5.25.

It was found that when 2-(dibenzylaminomethyl)cyclohexanone hydrochloride was heated at 95° in acetic acid solution for 2.5 hr. it, like the dihydrochloride of the corresponding disubstitution product, was decomposed almost completely with the formation of dibenzylamine hydrochloride in 90% yield.

2-(Methylbenzylaminomethyl)cyclohexanone hydrochloride. Cyclohexanone (15.0 g., 0.15 mole), 12.0 g. (0.076 mole) of

(19) This reversal also took place at room temperature and dimethyl cyclohexanone-2,6-dicarboxylate gradually precipitated from the aqueous solution.

(20) In a few instances the residue was obtained in a crystalline, acetone-insoluble form. The product was then refluxed with acetone for a short time and filtered.

(21) C. Mannich and P. Hönig (*Arch. Pharm.*, 265, 598 (1927)), b.p. 117° (24 mm.).

(22) C. Mannich and R. Braun [*Ber.*, **53**, 1874 (1920)], b.p. 100° (13 mm.); m.p. hydrochloride, 152°.

(23) Ref. 8, b.p. 90–94° (0.4 mm.).

methylbenzylamine hydrochloride,[24] 2.3 g. (0.076 mole) of paraformaldehyde and 30 ml. of acetic acid were heated at 75–80° for 2.5 hr. After removal of the acetic acid under reduced pressure, the oily residue was dissolved in 50 ml. of acetone. The product precipitated upon the addition of ether; yield 15.0 g. (75%); m.p. 145–146°[25] after recrystallization from acetone.

Anal. Calcd. for $C_{15}H_{22}ONCl$: C, 67.28; H, 8.28; N, 5.23; Cl, 13.24. Found: C, 67.24; H, 8.32; N, 5.36; Cl, 13.02.

2,6-Bis(methylaminomethyl)cyclohexanone dihydrochloride (compound 4) by debenzylation of compound 13. A mixture of 6.5 g. of compound 13, 3.0 g. of 5% palladium on cabon[26] and 150 ml. of absolute ethanol was hydrogenated under an initial pressure of 55 pounds for 9 hr. After filtration, the solvent was removed and the oily residue was dissolved in isopropyl alcohol. Upon the addition of ether the hygroscopic product precipitated.

2-(Methylaminomethyl)cyclohexanone hydrochloride. A mixture of 7.0 g. of 2-(methylbenzylaminomethyl)cyclohexanone hydrochloride, 3.0 g. of 5% palladium on carbon, and 150 ml. of absolute ethanol was hydrogenated under an initial pressure of 50 pounds for 15 min. The mixture was filtered and the solvent was removed under reduced pressure. The oily residue was dissolved in isopropyl alcohol and ether was added to precipitate the product; yield 3.6 g. (78%); m.p. 97–98°; m.p. 100–101° after recrystallization from isopropyl alcohol–ether.

Anal. Calcd. for $C_8H_{16}ONCl$: C, 54.08; H, 9.08; N, 7.88; Cl, 19.95. Found: C, 53.90; H, 9.02; N, 7.87; Cl, 19.55.

Oxime of 2-(methylaminomethyl)cyclohexanone hydrochloride. A solution was prepared from 1.0 g. of 2-(methylaminomethyl)cyclohexanone hydrochloride, 0.5 g. of hydroxylamine hydrochloride, 0.7 g. of potassium carbonate and 5 ml. of water. After 4 hr., the solution was saturated with potassium carbonate and extracted with ether. The ether solution was dried, treated with hydrogen chloride, and the precipitated oil was triturated with isopropyl alcohol whereupon it became crystalline; m.p. 192–193° (dec.) after recrystallization from methanol-ether; yield 0.4 g.

Anal. Calcd. for $C_8H_{17}ON_2Cl$: C, 49.87; H, 8.89; Cl, 18.40. Found: C, 49.67; H, 8.86; Cl, 18.58.

2-(Dimethylaminomethyl)cyclohexanone hydrochloride. In the preparation of this product, Mannich and Braun[22] used excess cyclohexanone as a solvent. It was found that a purer product was obtained when acetic acid was employed. A mixture of 19.6 g. (0.2 mole) of cyclohexanone, 3.0 g. (0.1 mole) of paraformaldehyde, 8.2 g. (0.1 mole) of dimethylamine hydrochloride and 40 ml. of acetic acid was heated on a steam bath for 2.5 hr. The solvent was removed, the solid residue was washed with acetone and filtered; m.p. 154–155°[27]; yield 14.5 g. (76%).

2,6-Bis(dimethylaminomethyl)cyclohexanone dihydrochloride (I) *from 2-(dimethylaminomethyl)cyclohexanone hydrochloride.* A mixture of 19.2 g. (0.1 mole) of 2-(dimethylaminomethyl)cyclohexanone hydrochloride, 3.0 g. (0.1 mole) of paraformaldehyde, 8.2 g. (0.1 mole) of dimethylamine hydrochloride, and 40 ml. of acetic acid was treated as described in the general procedure; yield 19.7 g. (69%); m.p. and mixed m.p. 176–177°.

2-(Dimethylaminomethyl)-6-(piperidinomethyl)cyclohexanone dihydrochloride. By the use of the general procedure, a mixture of 19.2 g. of 2-(dimethylaminomethyl)cyclohexanone hydrochloride, 3.0 g. of paraformaldehyde, 12.2 g. of piperidine hydrochloride, and 40 ml. of acetic acid yielded 15.5 g. (48%) of product; m.p. 166–167°; m.p. 168–169° after recrystallization from methanol-ether.

Anal. Calcd. for $C_{15}H_{30}ON_2Cl_2$: C, 55.35; H, 9.30; N, 8.61; Cl, 21.80. Found: C, 55.01; H, 9.44; N, 8.22; Cl, 21.43.

Dimethyl cyclohexanone-2,6-dicarboxylate (III). A mixture of 10.0 g. (0.4 g. atom) of magnesium, 1.0 g. of iodine, and 200 ml. of absolute methanol was cooled until the reaction subsided; it was then refluxed for 1 hr. on a steam bath. The mixture was cooled in an ice bath and 70 g. of dimethyl acetonedicarboxylate[28] (II) (0.4 mole) was added. After the mixture had been shaken thoroughly, it was refluxed for 1 hr., placed in a pressure bottle, and 80.0 g. (0.4 mole) of 1,3-dibromopropane was added. The mixture was heated for 24 hr. on a steam bath, the solvent was removed, and the oily residue was mixed with 125 ml. of concentrated hydrochloric acid which had been diluted with an equal volume of water. The product was extracted with ether, the solvent was removed from the extract, and the oily residue was dissolved in 250 ml. of boiling methanol; 130 ml. of water was then added. The solution was cooled and the precipitated product (16.8 g.) was filtered; a further amount (5.8 g.) was obtained by concentration of the filtrate to one half of its original volume. After the material had been washed with 60% methanol, it was dissolved in 340 ml. of boiling methanol and 200 ml. of water was added. From the cooled mixture, 21.5 g. (25%) of product was obtained; m.p. 142–143°.

Anal. Calcd. for $C_{10}H_{14}O_5$: C, 56.06; H, 6.59. Found: C, 56.07; H, 6.54.

Dimethylcyclohexanol-2,6-dicarboxylate. A mixture of 13.0 g. (0.06 mole) of dimethyl cyclohexanone-2,6-dicarboxylate, 0.3 g. of platinum dioxide, and 300 ml. of absolute methanol was hydrogenated for 1 hr. under an initial pressure of 50 pounds. After filtration of the mixture the solvent was removed from the filtrate. The oily residue was crystallized from petroleum ether (60–75°) and then recrystallized from the same solvent; m.p. 65–66°; yield 10.2 g. (78%).

Anal. Calcd. for $C_{10}H_{16}O_5$: C, 55.54; H, 7.46. Found: C, 55.60; H, 7.51.

Dimethyl 2,6-bis(dimethylaminomethyl)cyclohexanone-2,6-dicarboxylate dihydrochloride (IV). A mixture of 16.0 g. (0.074 mole) of dimethyl cyclohexanone-2,6-dicarboxylate, 12.0 g. (0.148 mole) of dimethylamine hydrochloride, 15.0 g. (0.185 mole) of 37% formalin, and 80 ml. of methanol was refluxed for 2 hr. The methanol and water were removed and the solid residue was refluxed with 60 ml. of acetone for 10 min. The cooled suspension was filtered and the product was washed with acetone; yield 26.8 g. (90%); m.p. 185–186°; m.p. 186–187° after recrystallization from methanol–ethyl acetate.

Anal. Calcd. for $C_{16}H_{30}O_5N_2Cl_2$: C, 47.89; H, 7.54; N, 6.98; Cl, 17.67. Found: C, 47.97; H, 7.66; N, 6.82; Cl, 17.75.

Dimethyl 2,6-bis(dimethylaminomethyl)cyclohexanol-2,6-dicarboxylate dihydrochloride. A mixture of 3.5 g. of dimethyl 2,6-bis(dimethylaminomethyl)cyclohexanone-2,6-dicarboxylate dihydrochloride (IV), 0.2 g. of platinum dioxide, and 50 ml. of acetic acid was hydrogenated at 60° under an initial pressure of 56 pounds for 5 hr. After removal of the catalyst and solvent, the oily residue was dissolved in hot isopropyl alcohol. The product, which precipitated from the cold solution, weighed 1.6 g. (46%); m.p. 205–206° (dec.) after recrystallization from methanol–ethyl acetate.

Anal. Calcd. for $C_{16}H_{32}O_5N_2Cl_2$: C, 47.64; H, 8.00; Cl, 17.58. Found: C, 47.75; H, 7.86; Cl, 17.30.

2,6-Bis(dimethylaminomethyl)cyclohexanone dihydrochloride (I). *Formation by hydrolysis and decarboxylation of* IV. A mixture of 3.0 g. (0.0075 mole) of IV and 27 ml. of 5% aqueous sodium hydroxide solution (0.034 mole) was stirred for 7 hr. Concentrated hydrochloric acid (4.0 g., 0.04 mole) was added, dropwise, whereupon carbon dioxide was evolved. The mixture was then made basic with sodium hydroxide solution, saturated with sodium chloride, and extracted with ether. The dried ether solution was treated with hydrogen chloride. The ether was decanted from the pre-

(24) F. F. Blicke and Chi-Jung Lu, *J. Am. Chem. Soc.*, **74**, 3933 (1952).

(25) A. L. Morrison and H. Rinderknecht [*J. Chem. Soc.*, 1510 (1950)] obtained the product in 54% yield by the use of alcohol as a solvent; m.p. 144–146°.

(26) Obtained from Baker and Company, Newark, N. J.

(27) Ref. 22, m.p. 152°.

(28) Purchased from Chas. Pfizer and Company.

cipitated oil and the latter was triturated with 20 ml. of isopropyl alcohol whereupon it crystallized; after filtration, 0.9 g. of product was isolated; m.p. 179–180°. A further amount (0.25 g.) of product was obtained by addition of ether to the isopropyl alcohol filtrate; total yield 54%. A mixture of the product and 2,6-bis(dimethylaminomethyl) cyclohexanone dihydrochloride, obtained from cyclohexanone, melted at 179–180°.

Anal. Calcd. for $C_{12}H_{26}ON_2Cl_2$: Cl, 24.85. Found: Cl, 24.50.

Oxime of 2,6-bis(dimethylaminomethyl)cyclohexanone dihydrochloride. Two samples of 2,6-bis(dimethylaminomethyl)cyclohexanone dihydrochloride (I), one obtained by the use of cyclohexanone, the other prepared by hydrolysis and decarboxylation of IV, were converted into oximes in the manner described below; both oxime salts, after recrystallization from methanol, melted at 221–222° (dec.); mixed m.p. 221–222° (dec.).

2,6-Bis(dimethylaminomethyl)cyclohexanone dihydrochloride (20.0 g., 0.07 mole), 20.0 g. (0.29 mole) of hydroxylamine hydrochloride, 30 ml. of pyridine, and 200 ml. of absolute ethanol were refluxed for 4 hr. The solvents were removed under reduced pressure, the residue was dissolved in a small amount of water, and the solution was made basic with sodium hydroxide. After saturation with sodium chloride, the mixture was extracted with ether. The dried ether solution was treated with hydrogen chloride; an oil precipitated. After decantation of the ether, the oil was heated with isopropyl alcohol whereupon it crystallized. After recrystallization from methanol-ether, the oxime dihydrochloride melted at 221–222° (dec.); yield 14.0 g. (67%).

Anal. Calcd. for $C_{12}H_{27}ON_3Cl_2$: C, 48.00; H, 9.07; Cl, 23.61. Found: C, 48.14; H, 8.98; Cl, 23.23.

2,6-Bis(dimethylaminomethyl)cyclohexanol dihydrochloride (V). A mixture of 25.0 g. of compound I, 225 ml. of methanol, and 0.25 g. of platinum dioxide was hydrogenated until the calculated amount of hydrogen was absorbed (4 hr.). The catalyst was removed and the solution was concentrated to one half of its original volume. Ether was added until the solution became cloudy. It was then cooled whereupon 19.0 g. (75%) of product precipitated; m.p. 229–230° (dec.); m.p. and mixed m.p. 231–232° (dec.)[16] after recrystallization from methanol-ether. The product was very hygroscopic.

The dipicrate, prepared in ethanol, melted at 198–199° after recrystallization from water; mixed m.p. 197–198°.[16]

Diphenylacetate of V. A mixture of the base, obtained from 5.0 g. of V, 40 ml. of methyl ethyl ketone, and 4.0 g. of diphenylacetyl chloride[29] was heated on a steam bath for 15 min. The precipitated product (3.5 g.) was filtered. Treatment of the filtrate with hydrogen chloride yielded an additional 3.0 g. After two recrystallizations from methanol-ether, the material melted at 246–247° (dec.); yield 3.8 g. (46%).

Anal. Calcd. for $C_{26}H_{38}O_2N_2Cl_2$: C, 64.86; H, 7.96; N, 5.82; Cl, 14.73. Found: C, 64.56; H, 8.11; N, 5.68; Cl, 14.40.

Diphenylchloroacetate of V. The base of V (4.4 g.), dissolved in 60 ml. of methyl ethyl ketone, was added, during a period of 1 hr., to a stirred solution of 5.5 g. of diphenylchloroacetyl chloride[30] dissolved in 60 ml. of methyl ethyl ketone. The mixture was heated for 15 min. on a steam bath. The precipitate (V) was removed by filtration. When the filtrate was treated with ethereal hydrogen chloride, an oil precipitated. The solvents were decanted and the oil was heated with isopropyl alcohol whereupon it became crystalline; yield 1.3 g.; m.p. 241–242° (dec.) after recrystallization from methanol-ether.

(29) J. S. Pierce, W. W. Haden, and R. D. Gano, *J. Am. Chem. Soc.*, **67**, 408 (1945).

(30) F. E. King and D. Holmes, *J. Chem. Soc.*, 166 (1947).

Anal. Calcd. for $C_{26}H_{37}O_2N_2Cl_3$: C, 60.52; H, 7.23; N, 5.43; Cl, 20.62. Found: C, 60.38; H, 7.41; N, 5.23; Cl, 20.55.

Benzilate of V. The base, obtained from 10.0 g. of V, was added with stirring, slowly and dropwise, to 9.3 g. of molten diphenylchloroacetyl chloride which was cooled in an ice bath. The mixture was then heated on a steam bath for 10 min., 25 ml. of water was added to the cooled mixture, and it was then acidified with hydrochloric acid. The oily material was extracted with ether and the ether solution was discarded. The aqueous solution was made alkaline with sodium hydroxide, the mixture was extracted with ether, and the dried extract was treated with hydrogen chloride. The precipitated, hygroscopic salt was recrystallized from methanol-ether; yield 7.0 g. (50%); m.p. 254° (dec.).

Anal. Calcd. for $C_{26}H_{38}O_3N_2Cl_2$: C, 62.76; H, 7.70; N, 5.63; Cl, 14.25. Found: C, 62.74; H, 7.82; N, 5.53; Cl, 14.02.

A sample of the base of V, which had been prepared from VI,[16] was converted into the benzilate in the manner described above; m.p. and mixed m.p. 254° (dec.).

2,6-Bis(dimethylaminomethyl)-1-phenylcyclohexanol. (a) 2,6-Bis(dimethylaminomethyl)cyclohexanone (42.4 g.) was added, dropwise, to a stirred solution of phenylmagnesium bromide which had been prepared from 63.0 g. of bromobenzene, 9.7 g. of magnesium and 1500 ml. of ether. The mixture was refluxed for 2 hr., decomposed with ammonium chloride solution, the ether layer was separated, washed with water, and the solvent was removed. The residue was distilled; b.p. 136–138° (0.1 mm.); yield 21.5 g. (37%).

Anal. Calcd. for $C_{18}H_{30}ON_2$: C, 74.44; H, 10.41. Found: C, 74.54; H, 10.36.

The dihydrochloride, obtained by the use of ethereal hydrogen chloride, melted at 269–270° (dec.) after recrystallization from isopropyl alcohol-ethyl acetate.

Anal. Calcd. for $C_{18}H_{32}ON_2Cl_2$: C, 59.50; H, 8.88; N, 7.71; Cl, 19.52. Found: C, 59.30; H, 8.91; N, 7.67; Cl, 19.17.

The dipicrate, prepared in ethanol, melted at 195–196° after recrystallization from ethanol.

Anal. Calcd. for $C_{30}H_{36}O_{15}N_8$: C, 48.13; H, 4.85. Found: C, 48.25; H, 4.97.

(b) A stirred solution of phenyllithium, prepared from 47.0 g. of bromobenzene, 4.2 g. of lithium, and 500 ml. of ether, was cooled to −5° and 59.3 g. of 2,6-bis(dimethylaminomethyl)cyclohexanone, dissolved in 100 ml. of ether, was added. The mixture was stirred for 1 hr., cooled and decomposed with saturated ammonium chloride solution. The ether layer was separated, washed with water, dried, and the solvent was removed. The oily residue was distilled; b.p. 128–131° (0.3 mm.); yield 45 g. (55%). The solidified product was recrystallized from petroleum ether (60–75°); m.p. 71–73°.

The dihydrochloride, prepared by the use of ethereal hydrogen chloride, melted at 276–277° (dec.) after recrystallization from isopropyl alcohol-ethyl acetate; mixed m.p. 275–277° (dec.).

The dipicrate, after recrystallization from ethanol, melted at 201–202°.

The base, dissolved in ether, was treated with excess methyl bromide. After several hours, the dimethobromide precipitated; m.p. 301–302° (dec.) after recrystallization from isopropyl alcohol and then from methanol-ether.

Anal. Calcd. for $C_{20}H_{36}ON_2Br_2$: C, 50.02; H, 7.56; Br, 33.27. Found: C, 49.99; H, 7.69; Br, 33.05.

The dimethiodide was obtained in a similar manner from the base and methyl iodide; m.p. 283–284° (dec.) after recrystallization from isopropyl alcohol and then from methanol-ether.

Anal. Calcd. for $C_{20}H_{36}ON_2I_2$: C, 41.82; H, 6.32; I, 44.19. Found: C, 41.91; H, 6.32; I, 44.40.

2,6-Bis(dimethylaminomethyl)-1-phenyl-1-propionyloxycyclohexane dihydrochloride. A mixture of 8.0 g. of 2,6-bis(dimethylaminomethyl)-1-phenylcyclohexanol dihydrochlo-

ride and 80 ml. of propionic anhydride was heated at 110–120° for 6 hr. and the excess anhydride was then removed. The oily residue was dissolved in about 100 cc. of hot acetone and the solution was cooled whereupon the product precipitated; yield 8.1 g. (88%); m.p. 228–229° after recrystallization from isopropyl alcohol-ethyl acetate.

Anal. Calcd. for $C_{21}H_{36}O_2N_2Cl_2$: C, 60.13; H, 8.65; N, 6.68; Cl, 16.90. Found: C, 59.95; H, 8.44; N, 7.02; Cl, 16.55.

The dimethobromide, prepared from the base in ether, melted at 220–221° (dec.) after recrystallization from isopropyl alcohol–ether.

Anal. Calcd. for $C_{23}H_{40}O_2N_2Br_2$: C, 51.50; H, 7.52; Br, 29.80. Found: C, 51.60; H, 7.59; Br, 29.85.

2,6-Bis(dimethylaminomethyl)-1-(2-pyridyl)cyclohexanol. A solution of butyllithium was prepared from 2.8 g. of lithium, 27.5 g. of butyl bromide, and 400 ml. of ether at −10° under nitrogen. The solution was cooled to −60°, stirred, and 28.5 g. of 2-bromopyridine, dissolved in 50 ml. of ether, was added during a period of 10 min. The stirred solution was maintained at −60° and 34 g. of 2,6-bis(dimethylaminomethyl)cyclohexanone, dissolved in 100 ml. of ether, was added during a 15-min. period. The material was stirred at −40° for 2 hr., the temperature was allowed to rise to room temperature and the mixture was decomposed with ammonium chloride solution. The ether layer was separated, dried, and the solvent was removed. The oily residue was distilled; b.p. 130–133° (0.1 mm.)[31]; yield 19.0 g. (41%). After the product became crystalline, it was recrystallized from petroleum ether (60–75°); m.p. 66–67°.

Anal. Calcd. for $C_{17}H_{29}ON_3$: C, 70.07; H, 10.03. Found: C, 70.11; H, 10.07.

When the base, dissolved in acetone, was treated with hydrogen chloride, the trihydrochloride precipitated. After recrystallization from isopropyl alcohol and then from methanol–ethyl acetate, the salt melted at 258–259° (dec.).

Anal. Calcd. for $C_{17}H_{32}ON_3Cl_3$: C, 50.94; H, 8.05; N, 10.49; Cl, 26.54. Found: C, 50.74; H, 7.96; N, 10.25; Cl, 26.95.

2,6-Bis(dimethylaminomethyl)-1-(2-pyridyl)-1-propionyloxycyclohexane dihydrochloride. A mixture of 10.0 g. of 2,6-bis(dimethylaminomethyl)-1-(2-pyridyl)cyclohexanol trihydrochloride and 100 ml. of propionic anhydride was heated at 110–120° for 12 hr. After filtration, the excess anhydride was removed and the residue was purified by refluxing it with 100 ml. of acetone in which the product did not dissolve. The filtered material (7.6 g., 67%) was recrystallized from methanol–ethyl acetate–ether; m.p. 249–250° (dec.).

Anal. Calcd. for $C_{20}H_{35}O_2N_3Cl_2$: C, 57.15; H, 8.39; N, 9.98; Cl, 16.87. Found: C, 57.08; H, 8.36; N, 9.71; Cl, 16.63.

2,6-Bis(dimethylaminomethyl)-1-aminocyclohexane tripicrate. The base of the oxime, obtained from 12.0 g. of the oxime of I, was dissolved in 125 ml. of ether. The solution was added, dropwise, to a stirred suspension of 6.1 g. of lithium aluminum hydride in 200 ml. of ether. The mixture was stirred and refluxed for 4 hr. and then stirred for 9 hr. at room temperature. Water (12 ml.) was added, dropwise, to the stirred mixture and then 6 ml. of 15% sodium hydroxide solution was added. After filtration, the dried ether filtrate was treated with hydrogen chloride. The crystalline, very hygroscopic precipitate (10.5 g.) was dissolved in ethanol and picric acid, dissolved in the same solvent, was added. The precipitated tripicrate was recrystallized from water; m.p. 230–231° (dec.).

(31) Ref. 8, b.p. 140–155° (0.5 mm.).

Anal. Calcd. for $C_{30}H_{36}O_{21}N_{12}$: C, 40.01; H, 4.03. Found: C, 40.05; H, 4.28.

2,5-Bis(dimethylaminomethyl)cyclopentanol dihydrochloride. A solution of 5.0 g. of 2,5-bis(dimethylaminomethyl)-cyclopentanone dihydrochloride in 8 ml. of water was added, dropwise, during a period of 20 min. to a stirred, cooled solution of 1.6 g. of sodium borohydride in 8 ml. of water. The mixture was stirred for 2 hr., decomposed with excess sodium hydroxide solution and extracted with ether. The dried ether solution was treated with hydrogen chloride and the precipitated salt was recrystallized from ethanol; yield 4.0 g. (80%); m.p. 226–228°.

Anal. Calcd. for $C_{11}H_{26}ON_2Cl_2$: C, 48.33; H, 9.59; N, 10.25; Cl, 25.94. Found: C, 48.29; H, 9.52; N, 9.97; Cl, 25.67.

Mannich reversal of dimethyl 2,6-bis(dimethylaminomethyl)-cyclohexanone-2,6-dicarboxylate dihydrochloride (IV). (a) After 15.0 g. of IV, 0.2 g. of platinum dioxide, and 150 ml. of absolute methanol had been hydrogenated for 1 hr. under an initial pressure of 50 pounds, the mixture was filtered, about one half of the solvent was removed, ether was added, and the mixture was placed in a refrigerator for 7 days. The precipitate (5.5 g.) of crude dimethyl 2,6-bis-(dimethylaminomethyl)cyclohexanol-2,6-dicarboxylate dihydrochloride was filtered and recrystallized five times from methanol–ethyl acetate; yield 1.8 g. (12%); m.p. 201–202° (dec.); mixed m.p. 205–206° (dec.).

The filtrate was concentrated to a small volume and cooled. The filtered precipitate (0.7 g.), dimethyl cyclohexanone-2,6-dicarboxylate, melted at 142–143°; mixed m.p. 142–143°. The filtrate, when treated with ether, yielded an oil which was dissolved in hot isopropyl alcohol. When the solution was cooled, 1.5 g. of trimethylamine hydrochloride was obtained; m.p. 274–275° (dec.) after recrystallization from isopropyl alcohol; mixed m.p. 276–277° (dec.). An aqueous solution of the trimethylamine hydrochloride was treated with picric acid; the m.p. and mixed m.p. of the precipitated picrate was 217–219°.

(b) A solution of 4.0 g. of dimethyl 2,6-bis(dimethylaminomethyl)cyclohexanone-2,6-dicarboxylate dihydrochloride in 25 ml. of water was heated on a steam bath for 3.5 hr. Throughout the experiment a stream of air, which passed through the mixture, carried the evolved formaldehyde into a solution of 2,4-dinitrophenylhydrazine.[32] At the end of 30 min., dimethyl cyclohexanone-2,6-dicarboxylate (1.0 g., 47%) (m.p. and mixed m.p. 141–142°), which had precipitated, was removed by filtration. The solvent was removed under reduced pressure and the oily residue was crystallized from isopropyl alcohol–ether and then recrystallized from isopropyl alcohol. This substance (0.3 g.) was dimethylamine hydrochloride; m.p. 167–168°; mixed m.p. 168–170°.

The precipitated 2,4-dinitrophenylhydrazone of formaldehyde (0.2 g.) was recrystallized from ethanol; m.p. and mixed m.p. 163–165°.[33,34]

ANN ARBOR, MICH.

(32) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *Systematic Identification of Organic Compounds*, 4th Ed. John Wiley and Sons, New York, N. Y., p. 219.

(33) N. R. Campbell [*Analyst*, **61**, 392 (1936)], m.p. 166°.

(34) In a duplicate experiment, a continuous stream of air was passed through the solution which was heated on a steam bath for 2 days. The precipitated hydrazone weighed 0.8 g.

[CONTRIBUTION FROM AVERY LABORATORY, UNIVERSITY OF NEBRASKA]

Benzacridines. II. Synthesis of Chlorinated 5,6-Dimethylbenz[*c*]acridines

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Received January 23, 1959

The generality of the synthesis of benz[*c*]acridines reported in the first paper of this series has been established by the preparation of 9-chloro-5,6-dimethylbenz[*c*]acridine and 10-chloro-5,6-dimethylbenz[*c*]acridine. The Pfitzinger-Borsche reaction was used to prepare 11-chloro-5,5-dimethyl-5,6-dihydrobenz[*c*]acridine, which was converted to 11-chloro-5,6-dimethylbenz[*c*]acridine. An abbreviated series of reactions leading to the parent compound, 5,6-dimethylbenz[*c*]acridine, has also been devised.

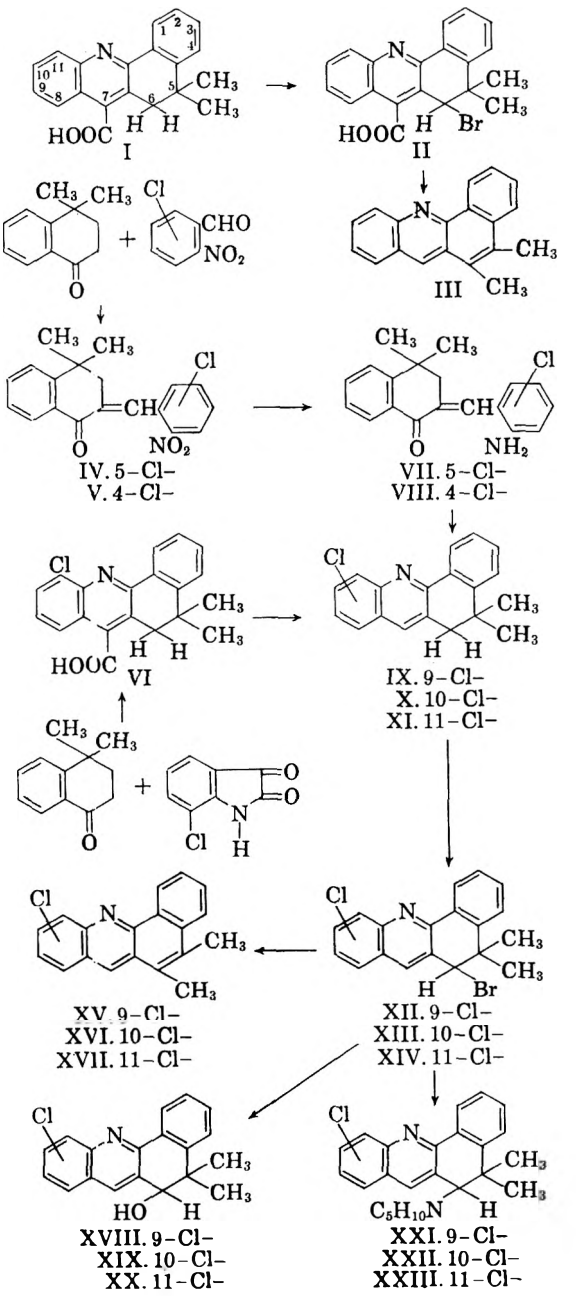
The first paper of this series[3] reported a new synthetic route leading to benz[*c*]acridines which are of interest as potential carcinogenic agents. In extending this work it was of considerable interest to prepare chlorinated benz[*c*]acridines, not only from the standpoint of the potential effect of the chlorine substituent on the carcinogenicity of the parent 5,6-dimethylbenz[*c*]acridine, but also as a test of the general utility of the new route to the preparation of substituted benz[*c*]acridines.

9-Chloro-5,6-dimethylbenz[*c*]acridine (XV) and 10-chloro-5,6-dimethylbenz[*c*]acridine (XVI) were prepared starting with suitably substituted aldehydes, using the general procedure reported previously[3] for the unsubstituted parent benzacridine. Both 5-chloro-2-nitrobenzaldehyde and 4-chloro-2-nitrobenzaldehyde condensed with 4,4-dimethyl-1-tetralone in acetic acid–sulfuric acid solvent to give 80% yields of the nitrobenzal tetralones IV and V. Reduction with iron and acetic acid gave a 90% yield of 4,4-dimethyl-2-(2-amino-5-chlorobenzal)-1-tetralone (VII) and 94% of the corresponding 4-chloro amino tetralone (VIII). Each was ring-closed in nearly quantitative yield to the chlorinated dihydrobenz[*c*]acridine derivatives IX and X.

A Pfitzinger-Borsche reaction of 7-chloroisatin and 4,4-dimethyl-1-tetralone was less satisfactory than the same reaction carried out with isatin,[3] but a 53% yield of the desired acid VI was obtained. This acid was then readily decarboxylated to 11-chloro-5,5-dimethyl-5,6-dihydrobenz[*c*]acridine (XI).

Bromination of the dihydrobenz[*c*]acridines IX, X, and XI was accomplished with *N*-bromosuccinimide in the manner reported previously for the unchlorinated compound. Thermal decomposition, involving a combined "α-dehydrobromination–Wagner rearrangement," gave the desired aromatized benzacridines XV, XVI, and XVII.

Hydrolysis of all three bromo compounds was effected with an aqueous sodium bicarbonate–dioxane solution to give the 6-hydroxy chlorinated dihydrobenz[*c*]acridines XVIII, XIX and XX in yields of 73–83%. Loss of the 9-chloro substituent[4]



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(3) V. L. Bell and N. H. Cromwell, *J. Org. Chem.*, **23**, 789 (1958).

(4) R. M. Acheson, *Acridines*, Interscience Publishers, Inc., New York, N. Y., 1956, p. 311.

was not realized under the mild conditions of hydrolysis. However, the ready displacement of the *p*-chlorine group was confirmed in preparing the 6-piperidino derivatives XXI, XXII, and XXIII. If an excess of piperidine was reacted with 6-bromo-9-chloro-5,5-dimethyl-5,6-dihydrobenz[*c*]acridine (XII), not only was the reactive bromine substituent replaced, but also much of the chlorine in the 9- position. Thus, the preparation of 9-chloro-5,5-dimethyl-6-*N*-piperidino-5,6-dihydrobenz[*c*]acridine (XXI) had to be carried out using only two molar equivalents of piperidine. Yields of the piperidino derivatives varied from 46–73% and considerable charcoal treatment was necessary to secure oil-free products.

An alternative route to the parent 5,6-dimethylbenz[*c*]acridine, somewhat simpler than the procedure reported previously,[3] was found to be quite satisfactory. Although 7-carboxy-5,5-dimethyl-5,6-dihydrobenz[*c*]acridine[3] (I), which was prepared via the Pfitzinger-Borsche reaction, appeared to be essentially insoluble in carbon tetrachloride, it was brominated in an 81% yield by refluxing a slurry of *N*-bromosuccinimide and the acid I in carbon tetrachloride. Upon melting the bromo acid II, decarboxylation along with "α - dehydrobromination" and methyl group rearrangement resulted, giving a 61% yield of 5,6-dimethylbenz[*c*]acridine (III). This offers a possibility for preparation of benz[*c*]acridines with substituents in the 8-, 9-, 10- and 11- positions where the suitably substituted isatin is more available than the *o*-nitrobenzaldehyde with the necessary substituent.

Discussion of ultraviolet spectra. A tabulation of the ultraviolet spectra of the benzacridines and intermediates is given in the Experimental section. Little change was noted upon introduction of chlorine into the parent 5,6-dimethylbenz[*c*]acridine.[3] Essentially identical spectra, regardless of substituents, were noted for the dihydro benzacridine derivatives and an extremely simplified spectral pattern was found for all dihydrobenzacridines bearing the 6-bromosubstituent. Thus, it appears that the completely aromatic benz[*c*]acridines can be readily distinguished from the dihydro benz[*c*]-acridines. However, differences in spectra between members of each class having different substituents are too subtle to be of value in identification.

EXPERIMENTAL[5]

6-Bromo-7-carboxy-5,5-dimethyl-5,6-dihydrobenz[c]acridine (II). A slurry of 7.15 g. (0.0236 mole) of the acid I,[3] 4.20 g. (0.0236 mole) of *N*-bromosuccinimide, 0.10 g. of benzoyl peroxide and 350 ml. of carbon tetrachloride was refluxed for 3.5 hr. At the end of this time all of the heavy NBS had changed to the light weight succinimide, which floated with the bromo acid on top of the solvent. The mixture was chilled and the solid was collected. The crude product was triturated thoroughly with cold water to remove the succinimide, after which the remaining solid was dissolved in acetone and the solution was treated with charcoal. Water was added to precipitate the bromo acid II in the form of colorless crystals, m.p. 196–198° (dec.). The yield was 7.30 g. (81%).

Anal. Calcd. for $C_{20}H_{16}NO_2Br$: C, 62.84; H, 4.22; N, 3.66. Found: C, 63.30; H, 4.77; N, 3.63.

5,6-Dimethylbenz[c]acridine (III). One g. (0.0026 mole) of the bromo acid II was melted in a small Erlenmeyer flask and heated carefully (200–210°) until the evolution of carbon dioxide and hydrogen bromide had ceased. The residue was cooled and extracted thoroughly with hot aqueous dioxane. The solution was neutralized with dilute sodium bicarbonate solution and cooled. The tan crystals were collected and recrystallized from aqueous acetone, with charcoal treatment. The yellow plates, 0.41 g. (61%), melted at 159–160°. A mixed melting point determination with authentic 5,6-dimethylbenz[c]acridine[3] showed the two products to be identical.

4,4-Dimethyl-2-(5-chloro-2-nitrobenzal)-1-tetralone (IV). A solution of 9.5 g. of 4,4-dimethyl-1-tetralone, 10.5 g. (0.0567 mole) of 5-chloro-2-nitrobenzaldehyde and 15 ml. of 95% sulfuric acid in 75 ml. of glacial acetic acid was allowed to stand at room temperature for 4 days. The precipitated crystals were recrystallized from glacial acetic acid to give 14.9 g. (80% yield) of light yellow crystals of the nitro ketone IV, m.p. 121–122°; λ_{max} 206, 275 mμ; ($\epsilon \times 10^{-3}$ 25.8, 23.7).

Anal. Calcd. for $C_{19}H_{16}NO_3Cl$: C, 66.76; H, 4.72; N, 4.10. Found: C, 66.76; H, 4.60; N, 4.08.

4,4-Dimethyl-2-(4-chloro-2-nitrobenzal)-1-tetralone (V). Using the same procedure outlined above for the 5-chloro isomer, a solution of 17.07 g. of 4,4-dimethyl-1-tetralone, 18.2 g. (0.0981 mole) of 4-chloro-2-nitrobenzaldehyde and 27 ml. of 95% sulfuric acid in 180 ml. of glacial acetic acid gave 26.9 g. (80% yield) of pale yellow crystals of the nitro ketone V, m.p. 150.5–151.5°; λ_{max} 206, 275 mμ; ($\epsilon \times 10^{-3}$ 25.0, 19.0).

Anal. Calcd. for $C_{19}H_{16}NO_3Cl$: C, 66.76; H, 4.72. Found: C, 66.66; H, 4.90.

7-Carboxy-11-chloro-5,5-dimethyl-5,6-dihydrobenz[c]acridine (VI). A solution of 7.55 g. (0.0416 mole) of 7-chloroisatin, 7.25 g. (0.0416 mole) of 4,4-dimethyl-1-tetralone, 8 g. of potassium hydroxide, 40 ml. of methanol and 20 ml. of water was refluxed for 24 hr. The solution was then cooled, diluted with 100 ml. of water, and acidified to methyl orange with hydrochloric acid. The crude acid was recrystallized once from ethanol and once from aqueous acetone, with charcoal treatment, to give 7.5 g. (53% yield) of pale yellow crystals of the acid VI, m.p. 240.5–242° (dec.); λ_{max} 213, 215, 227 (sho.), 265 (sho.), 272, 307, 320, 333, 349 mμ; ($\epsilon \times 10^{-3}$ 36.2, 35.8, 22.8, 32.2, 42.6, 8.40, 9.86, 12.0, 11.6).

Anal. Calcd. for $C_{20}H_{16}NO_2Cl$: C, 71.11; H, 4.77; Cl, 10.50. Found: C, 71.09; H, 4.88; Cl, 10.41.

4,4-Dimethyl-2-(2-amino-5-chlorobenzal)-1-tetralone (VII). A solution of 13.5 g. (0.0395 mole) of the nitro ketone IV in 250 ml. of glacial acetic acid and 40 ml. of water was heated on a steam bath and 5.5 g. of powdered iron was added over a period of 45 min. After heating an additional 15 min., the solution was cooled and poured over 1 l. of ice and water with rapid stirring. The yellow solid was collected, washed, and triturated thoroughly with water. Two recrystallizations from aqueous ethanol gave 11.1 g. (90% yield) of bright yellow crystals of the amino ketone VII, m.p. 151–153°.

Anal. Calcd. for $C_{19}H_{18}NOCl$: C, 73.19; H, 5.82; N, 4.49. Found: C, 73.10; H, 5.70; N, 4.37.

4,4-Dimethyl-2-(2-amino-4-chlorobenzal)-1-tetralone (VIII). The procedure described above for the preparation of the 5-chloro isomer (VII) was also used to prepare the 4-chloro isomer (VIII). Reduction of 25.8 g. (0.0755 mole) of the nitro ketone V in 500 ml. of glacial acetic acid and 75 ml. of

(5) Ultraviolet spectral determinations were made at about 25° using a Cary recording spectrophotometer, model 11 MS, using 95% ethanol solutions unless otherwise indicated.

water with 10.4 g. of powdered iron gave 22.05 g. (94% yield) of bright yellow crystals of the amino ketone VIII, m.p. 162–163°.

Anal. Calcd. for $C_{19}H_{18}NOCl$: C, 73.19; H, 5.82; N, 4.49. Found: C, 73.01; H, 5.79; N, 4.52.

9-Chloro-5,5-dimethyl-5,6-dihydrobenz[c]acridine (IX). A solution of 11.5 g. (0.0369 mole) of the amino ketone VII in 150 ml. of ethanol and 15 ml. of concentrated hydrochloric acid was heated for 1 hr. on a steam bath. The hot solution was treated with charcoal, filtered, and neutralized with dilute sodium hydroxide solution. The solution was diluted with water and cooled, precipitating pale yellow crystals. Recrystallization from aqueous acetone, with charcoal treatment, gave 10.0 g. (92% yield) of colorless plates of 9-chloro-5,5-dimethyl-5,6-dihydrobenz[c]acridine, m.p. 147–148°; λ_{max} 216, 226, 260 (sho.), 268, 319, 333, 349 mμ; ($\epsilon \times 10^{-3}$ 40.0, 37.8, 29.1, 38.3, 8.74, 14.5, 18.1).

Anal. Calcd. for $C_{19}H_{16}NCl$: C, 77.67; H, 5.49; N, 4.77; Cl, 12.07. Found: C, 77.79; H, 5.70; N, 4.71; Cl, 12.30.

10-Chloro-5,5-dimethyl-5,6-dihydrobenz[c]acridine (X). Ring closure of the amino ketone VIII was carried out using the procedure described above. From 22.05 g. (0.0707 mole) of VIII was obtained 20.0 g. (96% yield) of 10-chloro-5,5-dimethyl-5,6-dihydrobenz[c]acridine in the form of colorless plates, m.p. 131–132.5°; λ_{max} 213, 215, 230, 258 (sho.), 265, 299, 320, 335, 350 mμ; ($\epsilon \times 10^{-3}$ 41.7, 41.7, 32.0, 32.6 40.3, 9.00, 8.00, 13.4, 16.5).

Anal. Calcd. for $C_{19}H_{16}NCl$: C, 77.67; H, 5.49; N, 4.77. Found: C, 77.71; H, 5.68; N, 4.79.

11-Chloro-5,5-dimethyl-5,6-dihydrobenz[c]acridine (XI). The acid VI (8.8 g., 0.026 mole) was melted in a small Erlenmeyer flask and maintained at 245° until the evolution of carbon dioxide had ceased. After cooling, the residue was triturated with 10% potassium hydroxide solution and the alkaline mixture was extracted with ether. The ether layer was washed with water and the ether was evaporated. Two recrystallizations of the residue from aqueous acetone, with charcoal treatment, gave 6.1 g. (80%) of nearly colorless crystals, of XI, m.p. 124–125°; λ_{max} 211, 215, 227 (sho.), 263 (sho.), 270, 319, 332, 348 mμ; ($\epsilon \times 10^{-3}$ 35.5, 36.6, 25.5, 33.0, 43.6, 10.3, 13.4, 13.5).

Anal. Calcd. for $C_{19}H_{16}NCl$: C, 77.67; H, 5.49. Found: C, 77.70; H, 5.43.

6-Bromo-9-chloro-5,5-dimethyl-5,6-dihydrobenz[c]acridine (XII). A mixture of 5.87 g. (0.02 mole) of IX, 3.65 g. (0.02 mole) of *N*-bromosuccinimide and 0.05 g. of benzoyl peroxide in 75 ml. of carbon tetrachloride was refluxed for 2 hr. After cooling, the succinimide was removed by filtration and the solvent was removed under reduced pressure. The solid residue was recrystallized twice from aqueous acetone *at room temperature*, with charcoal treatment, to give 7.1 g. (95%) of colorless crystals of XII. The compound melted at 167.5–170° to a light yellow liquid, which decomposed to a bright red solid over the range 170–190°; λ_{max} (iso-octane) 211, 223, 235 (sho.), 273, 341, 355 mμ; ($\epsilon \times 10^{-3}$ 26.3, 29.2, 26.5, 36.7, 8.50, 8.34).

Anal. Calcd. for $C_{19}H_{15}NClBr$: C, 61.23; H, 4.06. Found: C, 61.44; H, 4.18.

6-Bromo-10-chloro-5,5-dimethyl-5,6-dihydrobenz[c]acridine (XIII). The procedure described above for the 9-chloro isomer was employed to brominate the 10-chloro isomer, giving a yield of 80% of colorless crystals of XIII, m.p. 155–157°. The molten yellow liquid changed sharply to a bright red solid at 166°. λ_{max} (iso-octane) 212, 219, 239, 267, 338, 346, 354 mμ; ($\epsilon \times 10^{-3}$ 27.7, 29.0, 25.0, 46.2, 9.00, 7.02, 10.0).

Anal. Calcd. for $C_{19}H_{15}NClBr$: C, 61.23; H, 4.06. Found: C, 61.72; H, 4.21.

6-Bromo-11-chloro-5,5-dimethyl-5,6-dihydrobenz[c]acridine (XIV). Use of the general bromination procedure resulted in a 90% yield of nearly colorless crystals of XIV, m.p. 180–182°; λ_{max} (iso-octane): 225, 275, 338, 354 mμ; ($\epsilon \times 10^{-3}$ 29.6, 43.8, 7.80, 6.48).

Anal. Calcd. for $C_{19}H_{15}NClBr$: C, 61.23; H, 4.06. Found: C, 61.13; H, 4.09.

9-Chloro-5,6-dimethylbenz[c]acridine (XV). The bromo compound XII, 1.50 g. (0.004 mole) was melted in a 10 ml. Erlenmeyer flask and kept at 200° for 10 min. The red solid was cooled and triturated with hot aqueous dioxane. The dioxane extract was neutralized with dilute sodium carbonate solution and cooled. The resulting solid was collected and recrystallized twice from acetone, with charcoal treatment. Another recrystallization, from benzene and petroleum ether, gave 0.80 g. (68% yield) of yellow needles of XV, m.p. 169–170°; λ_{max} 212, 224, 235, 279, 297, 372, 390 mμ; ($\epsilon \times 10^{-3}$ 25.0, 32.1, 34.8, 53.1, 49.1, 6.09, 5.56).

Anal. Calcd. for $C_{19}H_{14}NCl$: C, 78.21; H, 4.84. Found: C, 77.52, H, 4.90.

10-Chloro-5,6-dimethylbenz[c]acridine (XVI). Thermal decomposition of 1.50 g. of the bromo compound XIII at 165–175° resulted in a yield of 0.90 g. (77%) of 10-chloro-5,6-dimethylbenz[c]acridine (XVI) in the form of yellow needles, m.p. 170–171°; λ_{max} 212, 223, 230 (sho.), 272 (sho.), 281, 294, 324, 339, 357, 377, 394 mμ; ($\epsilon \times 10^{-3}$ 27.0, 35.6, 33.0, 43.2, 55.5, 58.0, 5.00, 5.36, 4.80, 5.60, 5.56).

Anal. Calcd. for $C_{19}H_{14}NCl$: C, 78.21; H, 4.84. Found: C, 78.01; H, 4.93.

11-Chloro-5,6-dimethylbenz[c]acridine (XVII). Thermal decomposition of the bromo compound XIV at 200° resulted in a 77% yield of bright yellow crystals of 11-chloro-5,6-dimethylbenz[c]acridine (XVII), m.p. 197–198°; λ_{max} 212, 224, 229 (sho.), 283, 293, 344, 374, 393 mμ; ($\epsilon \times 10^{-3}$ 28.4, 40.1, 38.4, 57.2, 54.9, 5.88, 5.92, 4.72).

Anal. Calcd. for $C_{19}H_{14}NCl$: C, 78.21; H, 4.84. Found: C, 78.07; H, 4.88.

9-Chloro-5,5-dimethyl-6-hydroxy-5,6-dihydrobenz[c]acridine (XVIII). A solution of 1.50 g. (0.004 mole) of the bromo compound XII in 20 ml. of dioxane and 10 ml. of 5% sodium bicarbonate solution was heated on a steam bath for 1 hr. Ten ml. of water was added and the solution was cooled. The oil which separated slowly solidified. The crude product was recrystallized, once from aqueous acetone with charcoal treatment, and once from ethanol. Colorless crystal, 1.03 g. (83% yield), were obtained, m.p. 190–192°; λ_{max} 218, 227, 262 (sho.), 269, 297, 310, 333, 348 mμ; ($\epsilon \times 10^{-3}$ 40.6, 38.1, 28.9, 33.8, 12.5, 10.0, 13.8, 17.2).

Anal. Calcd. for $C_{19}H_{16}NOCl$: C, 73.66; H, 5.21. Found: C, 73.52; H, 5.13.

10-Chloro-5,5-dimethyl-6-hydroxy-5,6-dihydrobenz[c]acridine (XIX). Treatment of 1.50 g. (0.004 mole) of the bromo compound XIII, as described for the 9-chloro isomer, gave 0.90 g. (73% yield) of the hydroxy compound XIX as colorless crystals, m.p. 166–167.5°; λ_{max} 212, 214, 228, 259 (sho.), 265, 318, 334, 349 mμ; ($\epsilon \times 10^{-3}$ 37.9, 38.7, 31.5, 33.6, 36.2, 7.96, 12.5, 15.2).

Anal. Calcd. for $C_{19}H_{16}NOCl$: C, 73.66; H, 5.21. Found: C, 73.35; H, 5.34.

11-Chloro-5,5-dimethyl-6-hydroxy-5,6-dihydrobenz[c]acridine (XX). Treatment similar to that described above for the 9- and 10-chloro isomers, using 1.50 g. of the bromo compound XIV, gave 1.0 g. (81% yield) of nearly colorless crystals of the hydroxy compound XX, m.p. 177–179°; λ_{max} 212, 216, 265 (sho.), 272, 319, 331 (sho.), 332, 347 mμ; ($\epsilon \times 10^{-3}$ 33.6, 34.8, 32.0, 38.6, 10.0, 12.2, 12.3, 11.4).

Anal. Calcd. for $C_{19}H_{16}NOCl$: C, 73.66; H, 5.21. Found: C, 73.73; H, 5.37.

9-Chloro-5,5-dimethyl-6-N-piperidino-5,6-dihydrobenz[c]acridine (XXI). To a solution of 1.50 g. (0.004 mole) of the bromo compound XII in 10 ml. of benzene was added a solution of 0.70 g. (0.008 mole) of piperidine in 5 ml. of benzene. The solution was refluxed for 2 hr. on a steam bath. After cooling the reaction mixture, the piperidine hydrobromide was removed, the filtrate extracted with water, and the benzene evaporated under reduced pressure. The solid residue was recrystallized once from aqueous acetone and once from ethanol, with charcoal treatment. Colorless crystals of the piperidino derivative XXI, 0.90 g. (60%

yield), were obtained, m.p. 139–140°; λ_{max} 217, 228 (sho.), 270, 336, 351 mμ; ($\epsilon \times 10^{-3}$ 43.3, 36.2, 36.0, 13.6, 14.2).

Anal. Calcd. for $C_{24}H_{25}N_2Cl$: C, 76.47; H, 6.69. Found: C, 76.56; H, 6.72.

10-Chloro-5,5-dimethyl-6-N-piperidino-5,6-dihydrobenz[c]-acridine (XXII). Treatment similar to that described for the 9-chloro isomer, but using an excess of piperidine, gave a 73% yield of the piperidino derivative XXII as pale yellow crystals, m.p. 148–150°; λ_{max} 217, 230 (sho.), 267, 337, 352 mμ; ($\epsilon \times 10^{-3}$ 44.0, 30.9, 37.5, 12.2, 13.0).

Anal. Calcd. for $C_{24}H_{25}N_2Cl$: C, 76.47; H, 6.69. Found: C, 76.05; H, 6.87.

11-Chloro-5,5-dimethyl-6-N-piperidino-5,6-dihydrobenz[c]-acridine (XXIII). This preparation was similar to that used for the 9-chloro isomer. However, three recrystallizations from acetone, with charcoal treatment, were necessary to obtain a pure product. From 1.50 g. of the bromo compound XIV was obtained 0.70 g. (46% yield) of colorless crystals of the piperidino derivative XXIII, m.p. 121.5–123°; λ_{max} 216, 273, 322, 335, 350 mμ; ($\epsilon \times 10^{-3}$ 40.9, 41.8, 10.0, 12.3, 11.1).

Anal. Calcd. for $C_{24}H_{25}N_2Cl$: C, 76.47; H, 6.69. Found: C, 76.73; H, 6.91.

Acknowledgment. This investigation was supported by a grant from the National Cancer Institute, U. S. Public Health Service, CY 2931.

LINCOLN, NEB.

[CONTRIBUTION FROM THE KEDZIE CHEMICAL LABORATORIES, MICHIGAN STATE UNIVERSITY]

A Study of Factors Influencing Catalytic Hydrogenation Kinetics[1]

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Received January 23, 1959

The rate of disappearance of hydrogen in the catalytic hydrogenation of benzene is found to obey the pseudo-first order rate law

$$-\frac{dp}{dt} = \frac{Rkp}{V_1/T_1 + V_2/T_2}$$

in which p is hydrogen pressure, t is time, R is the gas constant, V_1 and T_1 are the volume and absolute temperature of the reaction chamber, V_2 and T_2 are the volume and absolute temperature of the remainder of the apparatus, and k is the pseudo-first order rate constant. When $T_1 = T_2$ and $V_1 + V_2 = V$ (total volume of the apparatus), the expression reduces to

$$-dp/dt = RTkp/V$$

The rate of disappearance of benzene obeys the zero-order expression

$$c_0 - c = k_0 t$$

in which c_0 is the initial concentration of benzene, c is the concentration of benzene at time t, and k_0 is the zero-order rate constant. The relationship between k and k_0 is examined.

The rate of a catalytic hydrogenation is first-order with respect to hydrogen pressure, zero-order with substrate concentration, and directly proportional to the weight of the catalyst,[3] apparently conforming to the simple, pseudo-first order rate equation,

$$-dp/dt = k_{app}p \text{ or } \log p_0/p = k_{app}t/2.303 \quad (1)$$

in which p is the hydrogen pressure at time t, p_0 is the initial hydrogen pressure, and k_{app} is the apparent rate constant. In order to relate the rate constants to a unit quantity of catalyst, their experimental values are customarily divided by the weights of catalyst used.

When measured in terms of hydrogen pressure, the rate of catalytic hydrogenation also shows an apparent inverse relationship to the volume of the hydrogenation apparatus. In order to obtain rate constants which are independent of the apparatus volume, Fuzek and Smith[4] have suggested, on empirical grounds, a revised rate equation which includes this volume V:

$$-dp/dt = k'p/V \text{ or } \log p_0/p = k't/2.303V \quad (2)$$

This revised equation gives satisfactory comparisons of rate constants for low-pressure hydrogenations carried out in apparatus of different volumes but at similar pressures, and at or near room temperature. Recent investigations[5] have shown, however, that Equation 2 becomes less and less applicable as the reaction temperatures are increased; moreover, puzzling discrepancies arise when attempts are made to use Equation 2 for comparison of rates of the same hydrogenation measured in different pressure ranges under otherwise similar conditions.

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(1) Abstracted in part from the doctoral dissertation of Lyman R. Caswell, Michigan State University, 1956.

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In a review of methods of expressing the rates of gas reactions, Laidler[6] has pointed out that rates are commonly expressed in any of three ways: as disappearance of moles of reactant with time, dn/dt; as change of concentration with time, dc/dt; or as change of pressure with time, dp/dt. For ideal gases these methods of expression are interrelated through the equations $pV = nRT$ and $c = n/V$; these equations lead to a constant factor $1/V$ relating dc/dt to dn/dt at constant volume, and to a constant factor RT relating dp/dt to dc/dt at constant temperature. The $1/V$ factor is responsible for the observed dependence of the rate of pressure drop upon the apparatus volume, and the RT factor explains the failure of the empirically derived equation to apply satisfactorily in the comparison of rates of reactions at different temperatures. The best form of the rate expression to be used depends upon the experimental arrangement and the nature of the comparisons to be made. A rate expression is derived for the common experimental procedure in which the pressure change is measured for hydrogen in a reservoir connected to the hydrogenation bomb, which may or may not be at the reservoir temperature; the validity of the derived relationships is tested experimentally.

If ideal-gas behavior is an adequate approximation, then the number of moles n of hydrogen in the apparatus is given by

$$n = pV/RT \qquad (3)$$

in which R is the gas constant and T is the absolute temperature. Differentiation of this expression with respect to time gives the rate of disappearance of moles of hydrogen as a function of the rate of pressure drop at constant volume and temperature:

$$-dn/dt = -V/RT \times dp/dt \qquad (4)$$

If the rate of disappearance of moles of hydrogen is proportional to the hydrogen pressure, then

$$-dn/dt = kp \qquad (5)$$

Combination of Equations 4 and 5 then provides the relationship between the rate of pressure drop and the pressure itself:

$$-dp/dt = RT/V \times k_6 p \text{ or } \log p_0/p = (RT/2.303V)k_6 t \qquad (6)$$

When carrying out hydrogenations at elevated temperature, only the reaction chamber is normally heated, while the remainder of the apparatus is at room temperature. The total number of moles of hydrogen in this case is then

$$n = V_1 p/RT_1 + V_2 p/RT_2 = (V_1 T_1 + V_2 T_2)p/R \qquad (7)$$

where V_1 and T_1 are the volume and absolute temperature of the reaction chamber and V_2 and T_2 are the volume and absolute temperature of the remainder of the apparatus. For such cases, equation 6 becomes:

$$-dp/dt = Rk_8 p/(V_1/T_1 + V_2/T_2) \text{ or}$$
$$\log p_0/p = Rk_8 t/2.303(V_1/T_1 + V_2/T_2) \qquad (8)$$

In order to determine the applicability of Equations 6 and 8, the hydrogenation of benzene on platinum in glacial acetic acid was studied at low pressure in three different hydrogen voids over a range of temperatures. Analogous hydrogenations to those previously described were run at high pressure[7] with one void. In order to relate the rates of disappearance of benzene and of hydrogen, the rate of disappearance of benzene was independently determined for one set of low pressure conditions.

EXPERIMENTAL

Apparatus. Low-pressure hydrogenations were carried out with a modified Parr Model 3911 low-pressure hydrogenation apparatus. The pressure gage of the apparatus was replaced by a differential manometer with a 10-ft. scale ruled at 1-mm. intervals. Two special hydrogen reservoir tanks were constructed from $4^1/_2$ in. galvanized iron pipe. The total volumes of the apparatus with each tank were determined in a manner similar to that already described.[4] These volumes were: 4.615 l. for the apparatus with the standard Parr tank (large void), 1.698 l. (medium void), and 1.176 l. (small void).

The low pressure reaction chamber was a 250-ml. wide-mouth pressure bottle specially constructed by the H. T. Martin Co. of Evanston, Ill. The bottle was heated by a coil of No. 22 Nichrome wire wound around it. Temperature measurement was made by means of a copper constantan cold-junction thermocouple inserted into a thermocouple well in the stopper of the reactor bottle. The thermocouple was connected to a Weston millivoltmeter, and the temperature was controlled by means of a Variac connected to the heating coil. The average temperature variation throughout a hydrogenation was $\pm 0.6°$.

High pressure hydrogenations were carried out in an Aminco 50-ml. high pressure bomb manufactured by the American Instrument Co. The bomb was fitted with a glass liner composed of a Pyrex tube with a 10/30 standard taper joint and fitted with a perforated glass stopper. Temperature recording and control were made with a Micromax recording potentiometer connected to an iron constantan thermocouple inserted into the base of the bomb. Average temperature variation during a run was $\pm 1.0°$.

Materials. Matheson, Coleman, and Bell "thiophene-free" benzene was refluxed 24 hr. over sodium metal and fractionally distilled using a 20-plate column. The middle third, freezing point, 5.5°, and n_D^{25}, 1.4971, was reserved for hydrogenation. The American Petroleum Institute[8] reports freezing point at 5.333°, n_D^{25} 1.49792.

Baker's "analyzed" glacial acetic acid was used without further purification. All solvent samples used in the hydrogenations were taken from the same bottle.

Matheson, Coleman, and Bell cyclohexane was twice passed through a column of activated silica gel, using freshly activated silica gel with each pass. The purified cyclohexane showed no absorption when compared with distilled water at the benzene absorption maximum of 255 mμ.

(6) K. J. Laidler, "Kinetic Laws in Surface Catalysis," Chap. 4 in "Catalysis," Vol. I., P. H. Emmett, Ed., Reinhold Publishing Corp., New York (1954), p. 120.

(7) R. H. Baker and R. D. Schuetz, *J. Am. Chem. Soc.*, 69, 1250 (1947).

(8) American Petroleum Institute Research Project 44, "Selected Values of Properties of Hydrocarbons and Related Compounds," Carnegie Institute of Technology, Table 5a, October 31, 1950.

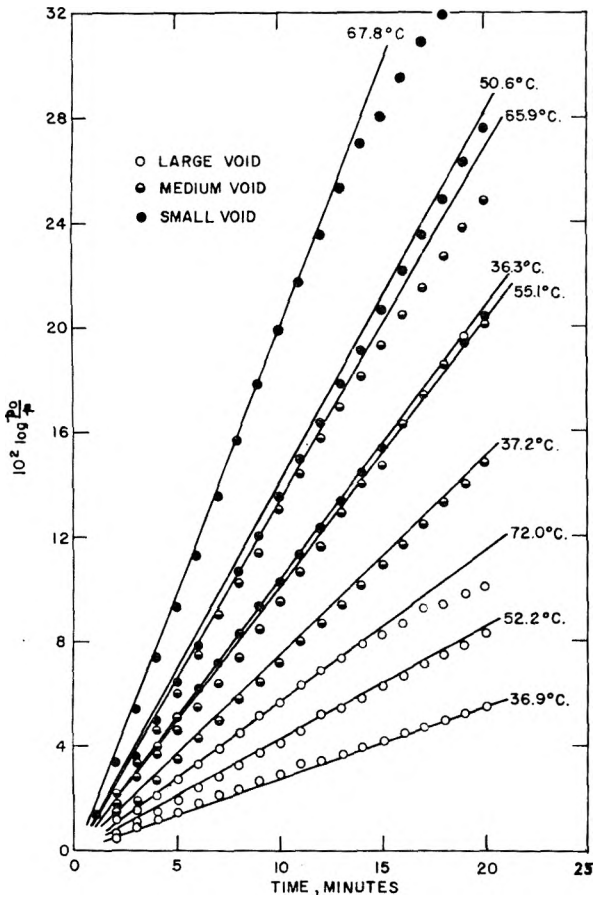


Fig. 1. Log p_0/p *vs.* time for various runs, showing effect of void on apparent rate constant at several temperatures

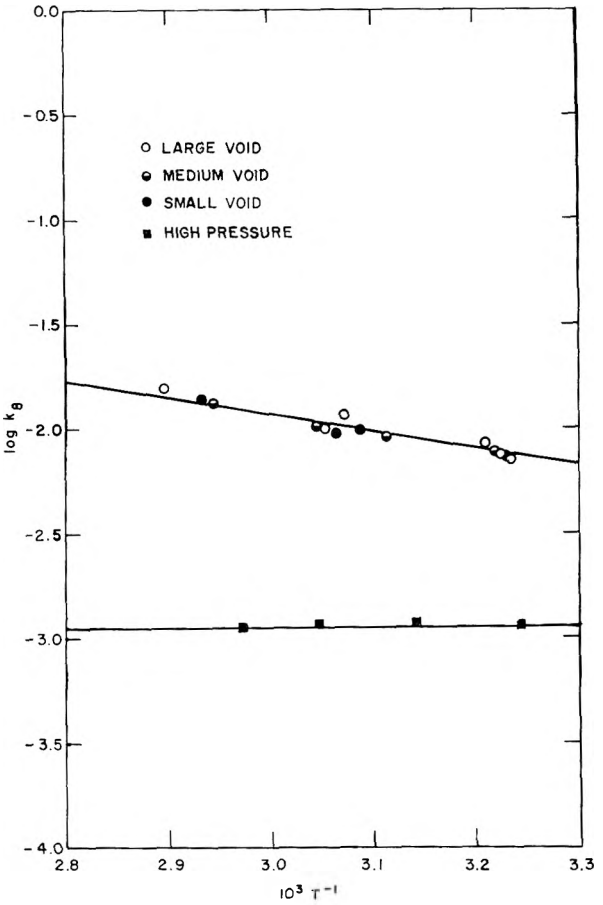


Fig. 2. Arrhenius plots of log k_8 *vs.* 1/T for low and high pressure runs

Hydrogen obtained from the Ohio Chemical and Surgical Co. was used without further purification.

Adams' platinum-oxide catalyst was obtained from the American Platinum Works. All hydrogenations were run with samples from the same batch of catalyst. Three samples of the catalyst were analyzed by reduction with hydrogen, giving an average platinum content of 79.45%. All rate constants were related to one gram of platinum by dividing them by the weight of platinum in the catalyst sample.

Hydrogenations. All low pressure hydrogenations were carried out with 4.4 g. (0.056 mole) of benzene in 10 ml. of glacial acetic acid, using 0.20 g. of platinum oxide and an average initial hydrogen pressure corresponding to a reading of 270 cm. of mercury on the differential manometer. High-pressure hydrogenations were carried out with exactly one-half these quantities of benzene, acetic acid, and catalyst, and using an initial hydrogen gage pressure of 1200 p.s.i. Pressure readings were made at 1-min. intervals during the course of each hydrogenation.

Determination of benzene. A series of low pressure hydrogenations using the largest void at 36.9° were stopped at various stages of partial hydrogenation and the reaction mixture was analyzed for residual benzene. The acetic acid was removed from the reaction mixture by two extractions of 4 ml. of the reaction mixture with 5-ml. portions of a saturated solution of sodium acetate. The hydrocarbon layer was diluted with cyclohexane and the benzene in it determined by means of the absorption at 255 mμ in a Beckman DU quartz spectrophotometer. The procedure was calibrated by use of a series of simulated hydrogenation mixtures to permit correction for the benzene lost during the extraction of the acetic acid.

DISCUSSION

Rate of disappearance of hydrogen. The values of log p_0/p were plotted against the time in minutes for all hydrogenations. The plots for nine such runs, clearly showing how void differences produce apparent differences in reaction rates, are depicted in Fig. 1. The slopes of the linear portions of these plots were determined by the method of least squares, and the values of k_{app}, k', k_6, and k_8 for Equations 1, 2, 6, and 8, respectively, were calculated from the slopes; these constants are presented in Table I. The Arrhenius plots of log k_8 *vs.* $1/T$ for the low and high pressure runs are shown in Fig. 2; the activation energy is found to be 4.3 kcal./mole at the lower pressures, and essentially zero kcal./mole in the high pressure runs.

The use of Equation 6 instead of Equation 8 leads to only a slightly higher activation energy, although the rate constants differ for the two equations. The importance of using Equation 8 becomes greater when the void and reaction chamber volumes are more nearly equal. As the reaction chamber volume becomes negligible relative to the void, Equation 8 reduces to Equation 6. In the low pressure runs reported, even the smallest void is enough larger than the reaction chamber to tend to mini-

TABLE I

RATE CONSTANTS FOR THE HYDROGENATION OF BENZENE

Temp.	Void, V, L.	10^2k_{app} Min.$^{-1}$ G.$^{-1}$	$10^2k'$ ($k' = k_{app}V$) L. Min.$^{-1}$ G.$^{-1}$	10^2k_6 ($k_6 = k_{app}V/RT$) Mole Atm.$^{-1}$ Min.$^{-1}$ G.$^{-1}$	10^2k_8 [$k_8 = k_{app}(V_1/T_1 + V_2/T_2)/R$] Mole Atm.$^{-1}$ Min.$^{-1}$ G.$^{-1}$
a. Low Pressure (Reaction Chamber Volume, 0.25 L.)					
35.8	4.60	3.78	17.4	0.709	0.746
36.3	1.16	15.2	17.6	0.716	0.868
36.9	4.60	3.99	18.4	0.749	0.788
37.2	1.68	11.0	18.5	0.752	0.860
38.4	4.60	4.50	20.7	0.843	0.887
48.1	1.68	13.4	22.5	0.909	1.04
50.6	1.16	20.7	24.0	0.966	1.16
52.2	4.60	6.23	28.7	1.16	1.22
53.1	1.16	20.1	23.3	0.937	1.13
54.1	4.60	5.24	24.1	0.981	1.03
55.1	1.68	15.0	25.2	1.02	1.16
65.9	1.68	19.6	32.9	1.32	1.49
67.8	1.16	29.3	34.0	1.35	1.61
72.0	4.60	8.37	38.5	1.56	1.63
b. High Pressure (Reactor Chamber Volume, 0.050 L.)					
35	0.04	32.6	1.30	0 0516	0.114
45	0.04	34.9	1.40	0.0534	0.116
55	0.04	36.4	1.46	0.0541	0.116
63	0.04	36.6	1.46	0.0530	0.112

mize the contribution of the correction introduced by Equation 8; even here, however, the correction does noticeably affect the magnitude reported for the rate constant, and the effect is much more pronounced at the higher pressures, where the void and reaction chamber volumes are comparable.

The striking differences in magnitude of the rate constants and the activation energies in the low and high pressure runs are not eliminated by the use of Equation 8. The lower rate constants at high pressure can most likely be attributed to the different shape of the adsorption isotherms for hydrogen on the catalyst surface in the different pressure ranges. The lower activation energy at high pressure suggests a difference in mechanism. A possible interpretation might be that the greater probability of occupancy by hydrogen of sites adjacent to benzene makes possible a lower energy activated complex. The present work does not make a definitive interpretation possible.

Rate of disappearance of benzene and its correlation with the rate of disappearance of hydrogen. The concentration of benzene, in moles per liter, remaining after time t, was found to be given by the zero-order rate equation,

$$c_0 - c = k_0 t$$

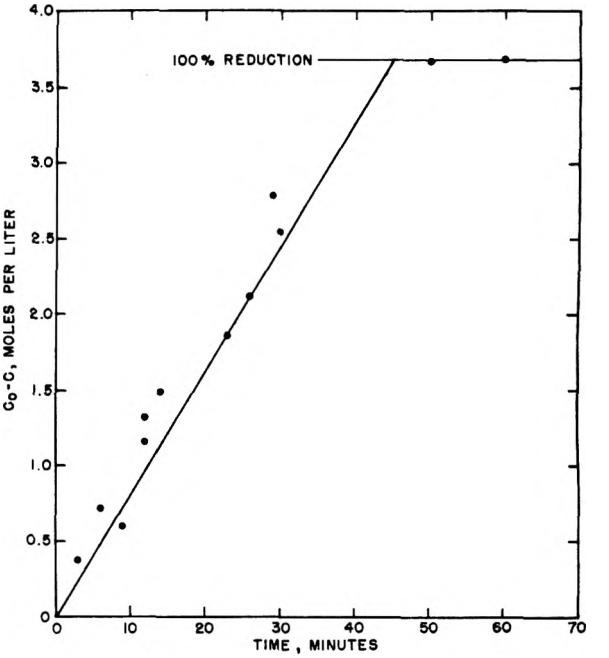


Fig. 3. Zero-order kinetics of benzene disappearance at 36.9° under hydrogen pressure of 3.31 atm.

in which c_0 is the initial concentration of benzene, c is the concentration of benzene which has reacted, and k_0 is the zero-order rate constant. The value of k_0 determined from the least-squares slope of the plot of $(c_0 - c)$ against t (Fig. 3) for 36.9° was 0.518 mole l.$^{-1}$ min.$^{-1}$ per gram of catalyst. Multiplication of this value by the volume of the reaction mixture, 0.016 l., gives 0.00828 mole min.$^{-1}$ g.$^{-1}$ According to the stoichiometry of the reaction, the average rate of disappearance of hydrogen should be three times the average rate of disappearance of benzene if the two rates are expressed in the same units. The rate constant for the hydrogenation for the same set of conditions was 0.00788 mole atm.$^{-1}$ min.$^{-1}$ g.$^{-1}$ Multiplying this constant by the average hydrogen pressure during the run, 251.3 cm., or 3.31 atm., gives the average rate of disappearance of hydrogen, 0.0261 mole min.$^{-1}$ g.$^{-1}$ Division of the average rate of disappearance of hydrogen by the average rate of disappearance of benzene gives a factor of 3.17 in good agreement with the stoichiometric expectations. This relationship cannot be obtained using the rate constant for hydrogen from either Equation 1 or Equation 2.

Acknowledgment. The authors are grateful to the Research Corp. for a Frederick Gardner Cottrell grant in support of this work.

LANSING, MICH.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF FLORIDA, AND NAVAL STORES STATION[1]]

p-Menthane Hydroperoxide[2]

J. S. STINSON, G. S. FISHER, AND J. E. HAWKINS

Received January 26, 1959

The oxidation of *cis*- and *trans*-*p*-menthane with oxygen to give *p*-menthane hydroperoxides has been studied. Both oxidized at the same rate to give similar mixtures containing the 1- and 8-monohydroperoxides and the 1,8 dihydroperoxide. In each case the 8-isomer obtained corresponded to the starting material and the 1-hydroperoxide was a mixture of the *cis* and *trans* isomers. The proportion of 1-hydroperoxides was greater in the case of *cis*-*p*-menthane which has an equatorial hydrogen in the 1- position. The maximum peroxide content obtainable in the oxidate under the conditions used was 25–35%. Elevated temperatures were required for rapid peroxidation and 130° was used for preparative work. For identification, the hydroperoxides were reduced to the corresponding alcohols. Except for *cis*-terpin, which was obtained pure, identification was based on infrared spectral data. *p*-Menthane hydroperoxide was found to undergo a first order thermal decomposition with an activation energy of 27 kcal. per mole.

For some time it has been known that *p*-menthane can be oxidized to a hydroperoxidic product which is an excellent initiator for low temperature copolymerization of butadiene-styrene.[3,4] Substantial quantities are now being manufactured and used in the production of synthetic rubber.

There is, however, no published data on the production, structure and properties of *p*-menthane hydroperoxide comparable in scope to the data on pinane-2-hydroperoxide.[5-7] The present investigation was undertaken to supply such information.

Discussion. Commercial limonene from citrus peel oil is a readily available material and is easily fractionated to give pure limonene, which yields a mixture of *cis*- and *trans*-*p*-menthanes which can be separated by fractional distillation.

In contrast to the marked difference in rates of oxidation of *cis*- and *trans*-pinane,[5] the rate of peroxide accumulation at 130° was essentially the same for *cis*- and *trans*-*p*-menthane. Both forms were much more resistant to oxidation than *cis*-pinane.[5] At 120° *trans*-*p*-menthane oxidized about one tenth as rapidly as *cis*-pinane.

The effect of temperature on peroxidation was studied using *trans*-*p*-menthane. As shown in Fig. 1, increasing the oxidation temperature makes a marked increase in the rate of peroxidation. Although the peroxide content obtained at 140° with *trans*-*p*-menthane was considerably higher than that obtained at the same temperature with pinane, reduction in oxidation temperature made only a small increase in the maximum peroxide content that could be obtained. The maximum peroxide content obtainable was about 25–30% in the temperature range of 120–140°. This figure dropped off to about 20% at 150° and increased only to about 35% even at 80°. The use of higher oxidation temperatures led to the production of larger amounts of acidic by-products. Thus, in the oxidations shown in Fig. 1, the acid numbers were 26 for the oxidate obtained at 140°, 17 for the oxidate obtained at 130°, and 14 for that obtained at 120°. It should be noted that at 140° the oxidation conditions used in this investigation led to very rapid decomposition of the peroxide after the maximum peroxide content was obtained.

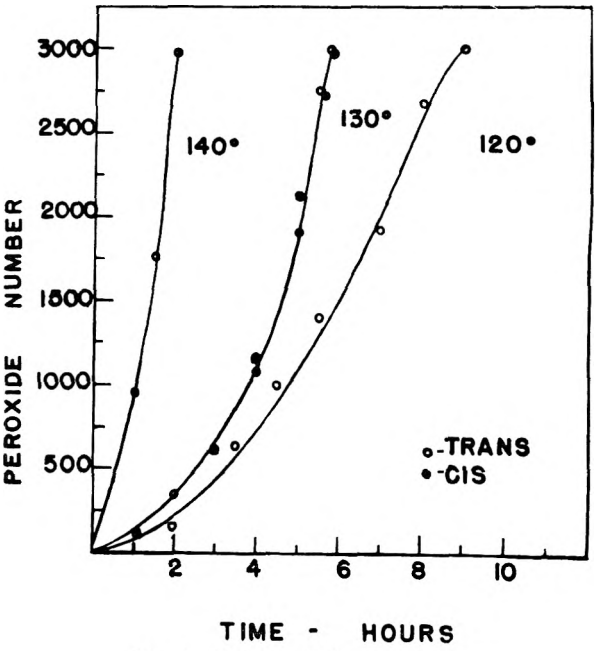


Fig. 1. Oxidation of *p*-menthane

(1) One of the laboratories of the Southern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.

(2) Taken in part from a thesis presented by J. S. Stinson to the graduate council of the University of Florida in partial fulfillment of the requirements for the degree of Master of Science. Presented at the Southeast Regional Meeting of the American Chemical Society, Gainesville, Fla., Dec. 11–13, 1958. Present address of J. S. S.: Newport Industries, Pensacola, Fla.

(3) G. S. Fisher, L. A. Glodblatt, I. Kneil, and A. D. Snyder, *Ind. Eng. Chem.*, **43**, 671 (1951).

(4) G. S. Fisher and L. A. Goldblatt (to Secretary of Agriculture), U. S. Patent **2,775,578** (1956).

(5) G. S. Fisher, J. S. Stinson, and L. A. Goldblatt, *J. Am. Chem. Soc.*, **75**, 3675 (1953).

(6) G. A. Schmidt and G. S. Fisher, *J. Am. Chem. Soc.*, **76**, 5426 (1954).

(7) G. S. Fisher, J. S. Stinson, R. N. Moore, and L. A. Goldblatt, *Ind. Eng. Chem.*, **47**, 1368 (1955).

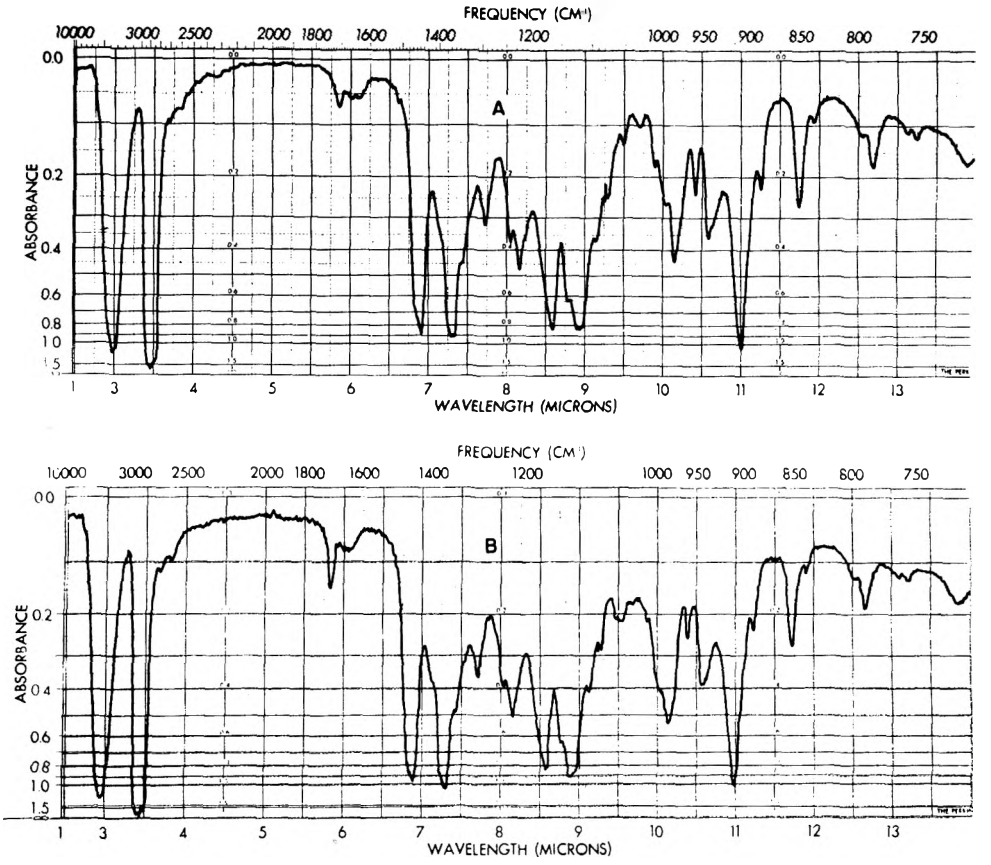


Fig. 2. Infrared spectra of mixed *p*-menthanols: A. 50% *trans*-*p*-Menthan-8-ol, 25% *cis*-*p*-menthan-1-ol, 25% *trans*-*p*-menthan-1-ol. B. Mixed *p*-menthanols from reduction of *trans*-*p*-menthane hydroperoxide

The most of the preparative portion of the present investigation, an operating temperature of 130° was selected as providing the best compromise between rapid oxidation and minimum amount of peroxide decomposition. Since the rate of peroxidation of the *p*-menthane is rather low until the peroxide number reaches about 500, the time required to prepare a batch of *p*-menthane hydroperoxide can be reduced by adding enough peroxide from a previous run to give an initial peroxide number of 500, or by initiating the oxidation at a higher temperature.[8]

Although direct oxidation failed to yield peroxide contents comparable to those obtained with pinane, high concentrations of *p*-menthane hydroperoxide were readily obtained by vacuum stripping using water vapor as a carrier gas. It was found advisable to wash the oxidate with sodium carbonate prior to concentration of the peroxide to remove acids formed during oxidation. These acidic products tended to catalyze decomposition of the hydroperoxide. *p*-Menthane oxidates containing about 25% of hydroperoxide yielded a concentrate containing about 84% of *p*-menthane hydroperoxide when stripped. These peroxide concentrates could be distilled at low pressures but satisfactory fractionation could not be obtained and there was considerable decomposition. The best method found for preparing *p*-menthane hydroperoxide of very high purity was the precipitation of the sodium salt from pentane solutions of either the concentrate or the distilled hydroperoxide followed by regeneration of the hydroperoxide with carbon dioxide. However, the yields by this process were poor. Hence, peroxide concentrates containing 80–85% or *p*-menthane hydroperoxide were used for reduction to alcohol.

In order to determine whether the peroxidation occurred predominantly at one of the three tertiary positions, as it does in the case of pinane, the hydroperoxides were reduced to the corresponding alcohols for comparison with known compounds. Liquid products were obtained in all cases. Attempts to separate solid alcohols by low temperature crystallization from pentane yielded about 6% by weight of *cis*-terpin in the case of the hydroperoxide from *trans*-*p*-menthane and a small amount of what appeared to be a mixture of terpins in the case of the hydroperoxide from *cis*-*p*-menthane. The amount of this latter alcohol was too small for purification and identification. Attempts to purify the crude alcohols by distillation removed small amounts of a ketonic impurity but the alcohols distilled over about a 3° range without any signifi-

(8) G. S. Fisher and L. A. Goldblatt (to Secretary of Agriculture), U. S.Patent **2,735,870** (1956).

cant fractionation. Attempts to prepare phenyl urethanes from the mixed alcohols were also unsuccessful.

Inasmuch as *cis*-terpin which has the same configuration as *trans*-*p*-menthane was isolated and identified, it was reasonable to assume that both the 1 and the 8 positions in the *p*-menthane molecule were peroxidized and that *trans*-*p*-menthan-1-ol and *trans*-*p*-menthan-8-ol[9] were the major components of the mixture of alcohols. The *cis* and *trans* forms of *p*-menthan-1-ol were available[10] as was *trans*-*p*-menthan-8-ol.[11] The infrared spectra of these compounds were compared with that of the reduced *trans*-*p*-menthane hydroperoxide. Most of the stronger bands were common to all four spectra but bands at 13.2, 13.1, 12.65, 11.25, 10.40 microns characteristic of *trans*-*p*-menthan-8-ol were obvious in the spectrum of the unknown and a broad, strong band at 8.9 microns suggested the presence of *cis*-*p*-menthan-1-ol as did a weak band at 7.75 microns.

The spectrum of a 50:50 mixture of these two alcohols was determined and found to be similar to that of the unknown but the bands at 7.75 and 8.9 microns were too strong and the general separation of bands was too good. The bands characteristic of *trans*-*p*-menthan-8-ol were of about the correct magnitude. Hence, the spectra of mixtures, containing 50:25:25 and 40:35:25 ratios of *trans*-*p*-menthan-8-ol, *cis*-*p*-menthan-1-ol, and *trans*-*p*-menthan-1-ol, respectively, were determined. The spectra of the 50:25:25 mixture is compared with that of the unknown alcohol in Fig. 2. The two are nearly identical but the *trans*-*p*-menthan-8-ol bands are a little strong and the *cis*-*p*-menthan-1-ol ones are a little weak. This situation was reversed in the other mixture. Hence, the monohydric alcohol from reduced *trans*-*p*-menthane hydroperoxide appears to be a mixture of about 45% *trans*-*p*-menthan-8-ol, 30% *cis*-*p*-menthan-1-ol, and 25% *trans*-*p*-menthan-1-ol. These figures should be regarded as only semiquantitative, particularly since the known mixtures all show less absorption than the unknown in the 9.4 to 10.3 micron region, and the possibility of some *p*-menthan-4-ol being present cannot be excluded.

Inasmuch as the hydrogenation conditions used were mild it seems safe to assume that the corresponding hydroperoxides were present in the same ratio. Hence, the 1 and 8 positions of *trans*-*p*-menthane are attacked at about equal rates and the addition of oxygen to the *p*-menthan-1-yl free radical is not very stereospecific. This is in contrast to the high degree of stereospecificity in the oxidation of pinane.[5]

The infrared spectrum of the alcohol from *cis*-*p*-menthane hydroperoxide was similar to that of the *trans*-alcohols. This mixture would be expected to contain *cis*-*p*-menthan-8-ol as well as the *cis*- and *trans*-*p*-menthan-1-ols. Attempts to prepare pure *cis*-*p*-menthan-8-ol, by hydrogenation of α-terpineol, for use in estimating the composition of the mixture gave only mixtures of the two isomers. Some idea of the spectrum of the *cis*-isomer was obtained by suitable compensation with the *trans*-isomer. The major bands in this spectrum corresponded to major bands in the spectrum obtained by similar compensation of the crude alcohols with a 6:5 mixture of *cis*- and *trans*-*p*-menthan-1-ols. The crude alcohol contained some additional bands due to a carbonyl impurity. A very rough approximation indicated that only about 30% of *cis*-8-ol was present. This predominance of the 1-isomers is reasonable because the equatorial 1-hydrogen of *cis*-*p*-menthane should be attacked more readily than the axial hydrogen of the *trans*-isomer while the ease of attack at the 8 position should be the same for both isomers.

In view of the difficulty experienced in obtaining high concentrations of *p*-menthane hydroperoxide by direct oxidation, it seemed desirable to make a brief study of the decomposition of an oxidate containing about 25% of the hydroperoxide. The oxidate used was prepared in the usual manner at 130° and the decomposition was followed iodometrically at 120° and 130°. The results are presented in Fig. 3. The first order reaction rate constants are 0.22 and 0.53 hr. $^{-1}$ corresponding to an activation energy 27 kcal./mole. Although the activation energy is the same as that observed for the decomposition of pinane hydroperoxide, the individual rates are much higher, than were obtained for pure pinane

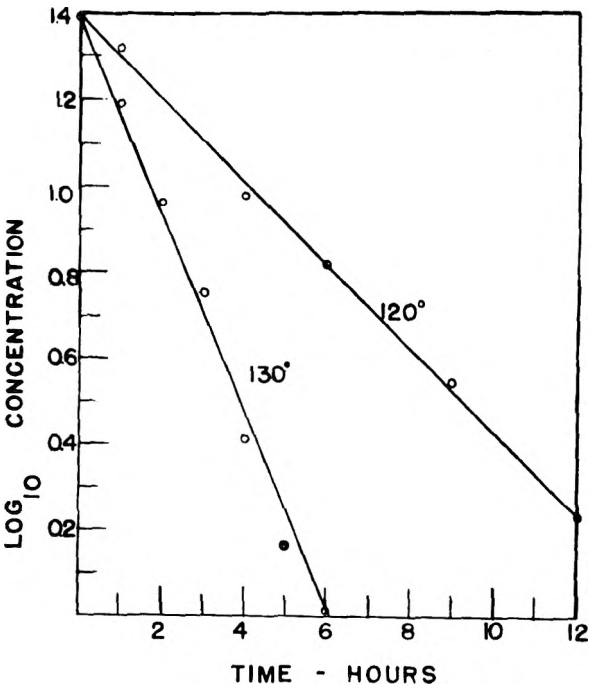


Fig. 3. Decomposition of *p*-menthane hydroperoxide from *trans*-*p*-menthane

(9) *cis*-Terpin is *trans*-*p*-menthan-1,8-diol.

(10) Prepared by Dr. G. A. Schmidt from β-terpineols kindly supplied by Dr. J. P. Bain of the Glidden Co.

(11) Kindly supplied by the Hercules Powder Co.

hydroperoxide.[12] The slower rate of oxidation of *p*-menthane and equal or greater rate of decomposition of the hydroperoxide at a given temperature is in accord with the low maximum peroxide content obtainable with *p*-menthane.

EXPERIMENTAL

p-Menthane. The *p*-menthane used in this work was prepared by hydrogenation of a commercial limonene using a nickel on filter aid catalyst at 100 atm. and 130°. The crude *p*-menthane, n_D^{20} 1.4422, d_4^{20} 0.8010, was subjected to a preliminary distillation at 20 mm. to remove low and high boiling impurities. The heart cut was then passed through a column of activated silica gel to remove small amounts of residual unsaturated compounds. The product purified in this manner was substantially pure *p*-methane (n_D^{20} 1.4409, d_4^{20} 0.8011), but was a mixture of *cis* and *trans* isomers.

This mixture was separated by fractional distillation at 20 mm. through a column rated at 100 plates. A reflux ratio of 100:1 was used for removal of the lower boiling *trans* form and this was decreased to 30:1 for the *cis* form. The physical constants of both the *trans-p*-menthane (b.p.$_{20\ mm.}$ 64°, d_4^{20} 0.7930, n_D^{20} 1.4369) and *cis-p*-menthane (b.p.$_{20\ mm.}$ 66°, d_4^{20} 0.8086, n_D^{20} 1.4433) were in excellent agreement with those reported by O'Connor and Goldblatt.[13] The assignment of configuration is based on the Auwers-Skita rule.

p-Menthane hydroperoxide. Samples of *p*-menthane, usually 100–250 ml., were oxidized in the conventional manner using reactors having a fritted-glass false bottom. The oxygen flow rate was varied within the range of 15–80 per hour and the temperature was varied within the range of 120–150°. During a given oxidation the temperature was held constant by immersing the reactor in a suitable liquid constant temperature bath and if necessary by use of a thermostatically controlled internal cooling coil.[7] Progress of the peroxidation was followed by determining the peroxide number of small samples withdrawn intermittently using the Wheeler method[14] as modified for terpenes.[5] To avoid excessive decomposition, preparative oxidations were stopped when the oxidate contained 20–25% hydroperoxide. In calculating percentage of *p*-menthane hydroperoxide present in the oxidates it was assumed that only the monohydroperoxide (peroxide number 11,620, 9.3% active oxygen) was formed.

In a typical preparation, oxidation of *cis-p*-menthane for 5.5 hr. at 130° gave an oxidate having a peroxide number of 3000. This product was washed with small portions of 3% aqueous sodium carbonate solution until free of acid. Vacuum steam stripping at a pressure of 0.3 mm. to a maximum pot temperature of 60° gave a peroxide concentrate having a peroxide number of 9800 (84%). The recovered *p*-menthane contained about 1% of peroxide and could be re-used without further purification.

The physical properties of typical peroxide concentrates (84%) prepared for the isomeric *p*-menthanes were: *cis* n_D^{20} 1.4686, d_4^{20} 0.966; *trans* n_D^{20} 1.4679, d_4^{20} 0.965.

A portion (20 g.) of the concentrated hydroperoxide from *cis-p*-menthane was dissolved in about 100 ml. of pentane. After cooling this solution in an ice bath, 8 g. of 50% sodium hydroxide was added dropwise with shaking, keeping the temperature below 5°. The precipitated salt of the hydroperoxide was filtered off, washed with pentane and with benzene, and suspended in benzene. This suspension was stirred vigorously with distilled water while a stream of carbon dioxide was passed through the mixture. After 30 min. the two layers were separated and the benzene layer was dried. After removal of the benzene under vacuum, 4.7 g. of *p*-menthane hydroperoxide, peroxide number 11,420, n_D^{20} 1.4689, d_4^{20} 0.967, was obtained. Treatment of the filtrate with additional sodium hydroxide yielded more precipitate but the peroxide regenerated from the second and third crops was less pure than the starting material.

A commercial sample of "pure" *p*-menthane was found to contain appreciable amounts of unsaturated compounds. These were removed by adsorption on silica gel. A 200-ml. sample of this was oxidized in a manner similar to that described above, but the oxidation was started at 145° to avoid or reduce the induction period. The oxidation temperature was reduced as the oxidation progressed.

Time, Min.	Peroxide No.	Temp. Reduced to
30	200	140
60	600	135
90	1100	130
150	2200	125
180	2600	120
240	3000	115
270	3200	—

The final oxidate was yellow and had an acid number of 13. A stripping distillation to a pot temperature of 85° at 0.3 mm. yielded 42 g. of yellow residue, peroxide number 9300, acid number 45. This product was dissolved in heptane, washed with base to remove the acids and recovered by stripping off the heptane. This treatment gave 34 g. of light yellow peroxide concentrate, peroxide number 9800. Distillation at 0.2–0.3 mm. gave 29 g. b.r. 68–80°. Neither the distillate or the residue had as high a peroxide number as the charge. The distillate was dissolved in 2 volumes of pentane and cooled in an ice bath and treated with half the stoichiometric amount of 50% sodium hydroxide solution. The precipitated sodium salt was washed with pentane and ether, suspended in ether, and stirred with a little water and solid carbon dioxide. From the ether layer 2 g. of product was isolated in the usual manner, n_D^{20} 1.4659, d_4^{20} 0.961, peroxide number 11,600.

Reduction of p-menthane hydroperoxide from trans-p-menthane. The method of reduction was essentially that of Lorand.[15] A concentrated, purified peroxide (47.7 g.) prepared from *trans-p*-menthane in the usual manner, peroxide number 9600 (83%), was added dropwise, over a 45-min. period, to a solution of 33 g. of sodium sulfide ($Na_2S{\cdot}9H_2O$) and 3.6 g. of 50% sodium hydroxide in approximately 70 ml. of water. The temperature was maintained between 50–60° for 2 hr., and at 70–80° until a final peroxide number of 400 was obtained. This required about 3 hr. The aqueous layer was separated from the alcohol layer after cooling, and the alcohol layer was washed with 50 ml. of water. Thirty-six g. of crude alcohol (n_D^{20} 1.4611) was obtained.

An additional 4.2 g. of terpene alcohol, n_D^{20} 1.4610, was obtained by extracting the aqueous layers with ether. Numberous attempts to separate crystals of the alcohol which formed in an ice bath were unsuccessful. When pentane was used as a solvent crystals were obtained which, after drying on a porous plate, melted 79–93°. Recrystallization gave 0.20 g. of alcohol, m.p. 97–103°. After drying by heating the capillary tube at 125–130° for 20 min., the alcohol recrystallized, m.p. 103.5–105°. Authentic *cis*-terpin melted at 104–105°. A mixed sample melted at 103–105°. This confirmed the presence of *cis*-terpin to the extent of about 6% in the reduction product.

(12) It should be noted that less pure samples of pinane hydroperoxide decomposed more rapidly.

(13) R. T. O'Connor and L. A. Goldblatt, *Anal. Chem.*, 26, 1726 (1954).

(14) D. H. Wheeler, *Oil & Soap*, 9, 89 (1932).

(15) E. J. Lorand (to Hercules Powder Co.), U. S. Patent 2,484,841 (1949).

Catalytic hydrogenation[5] of the hydroperoxide in ethyl acetate, using PtO_2 catalyst, produced a crude alcohol n_D^{20} 1.4612, which was similar to that obtained by sodium sulfide reduction. The hydroperoxide absorbed 1.01 moles of hydrogen per mole.

A portion of the alcohol mixture remaining after crystallization of *cis*-terpin was distilled at a pressure of 0.9 mm. of mercury. The first fraction (about 5%) had b.p. 48–54°, n_D^{20} 1.4561. This was primarily ketonic material and was discarded. The main fraction (about 72%) had b.p. 54–57°/0.9 mm. 207–209°/approximately 760 mm., n_D^{20} 1.4610. Infrared spectral data[16] (Fig. 2) indicated that this product was a mixture of *p*-menthanols with a trace of ketone (5.8 micron band). Attempts to obtain solid derivatives from it were unsuccessful.

Reduction of p-menthane hydroperoxide from cis-p-menthane. Preparation and reduction were carried out as described for the *trans* isomer. The crude reduction product was steam distilled to give a product having n_D^{20} 1.462, d_4^{20} 0.910 and an infrared spectrum quite similar to that of the product from *trans-p*-menthane. A small amount of non-steam volatile matter was recovered by ether extraction. After removal of the ether and addition of pentane, crystals melting at 115–130° were obtained. Recrystallization reduced the melting range to 122–124°. The amount was too small for further purification and identification.

Acidic oxidation products. Acidification of the sodium carbonate extracts obtained during preparation of the hydroperoxide and extraction with chloroform yielded a liquid product, neut. equiv. 208. Partition chromatographic analysis[17] of this material indicated the presence of both mono- and dicarboxylic acids. On the basis of a quantitative hypoiodite oxidation, only 60% of the monocarboxylic acid fraction was the methyl keto acid which would be expected as a decomposition product of *p*-menthane-1-hydroperoxide.

Thermal decomposition of p-menthane hydroperoxide. Thermal decomposition was carried out in the same manner as previously described for pinane hydroperoxide.[5] In the present case 0.3 g. samples of a *p*-menthane oxidate containing 25% of hydroperoxide by weight were used.

OLUSTEE, FLA.

(16) All spectra were obtained on the neat liquids using a Perkin-Elmer 21 spectrophotometer with NaCl optics and an 0.025 mm. cell.

(17) D. E. Baldwin, V. M. Loeblich, and R. V. Lawrence, *Anal. Chem.*, 26, 760 (1954).

[CONTRIBUTION FROM RESEARCH LABORATORIES OF S. B. PENICK AND COMPANY]

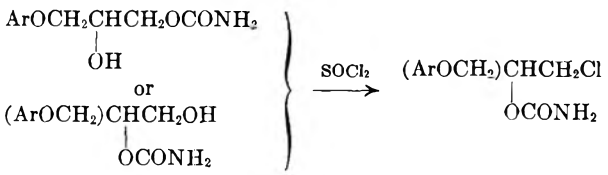
Rearrangement of Substituted 1,2-Glycol Monocarbamates and Related Reactions

JOHN R. CLARK AND MICHAEL PUGLIESE

Received January 29, 1959

The influence of substituents on the rearrangement of β-hydroxyethylcarbamates in the presence of thionyl chloride is discussed. Analogous reactions of epoxides in strongly acid media are related.

It was recently shown that structurally isomeric β-hydroxyethylcarbamates react with $SOCl_2$ to give the same β-chloroethylcarbmate through rearrangement of one of the isomers.[1] This rearrangement has now been confirmed by several more examples. (Table I)

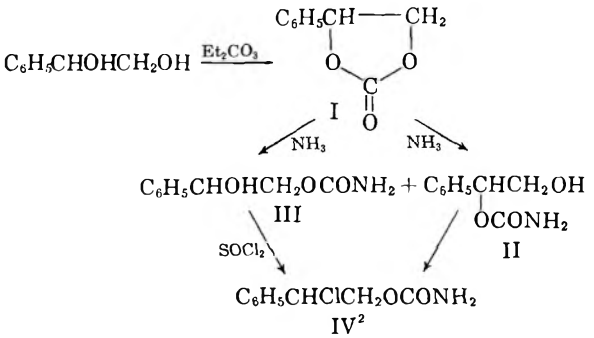


Further investigation of the generality of this process, however, revealed that the nature of the substituent in β-hydroxyethylcarbamates determined the position of the chloro group formed by reaction with thionyl chloride. When the substituent was phenyl, the rearrangement occurred to give the chlorocarbamate in which the chlorine was attached to a secondary carbon atom.

The synthetic method was the same as was previously described.[1]

(1) M. M. Baizer, J. R. Clark and J. Swidinsky, *J. Org. Chem.*, 22, 1595 (1957).

CHART I



The importance of the substituent in β-hydroxyethylcarbamates, as shown in Chart I, was emphasized by contrast with our previous experience.[1] In that case, rearrangement of the primary carbamate occurred and was assumed to result from addition of the chloride ion to the primary carbon atom of a carbonium ion intermediate, but in both instances a chlorosulfite intermediate is presumably decomposed to give the carbonium ion.[1]

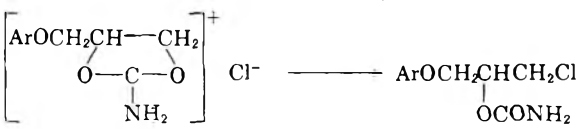
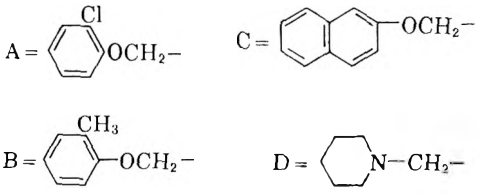
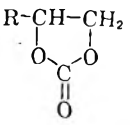


TABLE I



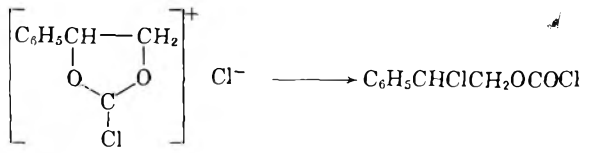
Section I



R	Formula	M.P., °C.	Analyses							
			Calcd.				Found			
			C	H	N	Cl	C	H	N	Cl
IA	$C_{10}H_9ClO_4$	109.0–109.3	52.52	3.93			53.15	3.96		
IB[a]		95.4–96.0								
IC	$C_{14}H_{12}O_4$	127.0–127.5	68.84	4.95			69.23	5.09		
ID[b]	$C_9H_{16}NO_3$		58.35	8.16	7.56		60.17	8.51	8.14	
		Section II								
		$RCH(OCONH_2)CH_2OH$								
IIA	$C_{10}H_{12}ClNO_4$	123.2–123.5	48.87	4.92	5.70		49.49	5.01	6.07	
IIB	*$C_{11}H_{15}NO_4$*	*115.0–115.6*	*58.65*	*6.71*	*6.22*		58.82	6.69	6.58	
IIC	$C_{14}H_{15}NO_4$	150.8–151.0	64.36	5.79	5.36		64.38	5.70	5.68	
IID[c]	$C_9H_{19}ClN_2O_3$	170.0–171.0	45.70	8.02	11.32		45.34	8.16	11.47	
		Section III								
		$RCHOHCH_2OCONH_2$								
IIIA	$C_{10}H_{12}ClNO_4$	98.4–98.8	48.87	4.92	5.70		48.99	5.16	5.74	
IIIB[d]		92.0–93.0								
IIIC	$C_{14}H_{15}NO_4$	144.5–145.0	64.36	5.79	5.36		64.40	5.86	5.88	
IIID	$C_9H_{18}N_2O_3$	121.5–122.0	53.39	8.97	13.85		52.99	8.79	13.71	
		Section IV								
		$RCH(OCONH_2)CH_2Cl$								
IVA	$C_{10}H_{11}Cl_2NO_3$	81.2–82.0	45.45	4.17	5.30		45.72	4.35	5.48	
IVB	$C_{11}H_{14}ClNO_3$	87.2–88.0	54.21	5.79	5.75	14.55	54.36	6.04	5.68	14.30
IVC	$C_{14}H_{14}ClNO_3$	125.5–126.0	60.11	5.05	5.01	12.67	60.05	5.01	4.45	12.05
IVD[e]	$C_9H_{17}ClN_2O_2 \cdot H_2O$	142–143	45.69	8.02	11.73	14.85	45.56	7.84	11.57	15.20

[a] Described by B. J. Ludwig and E. C. Piech, *J. Am. Chem. Soc.*, **73**, 5894 (1951). [b] A redistilled oil, b.p. 130–132° (0.5 mm.), n_D^{20} 1.4798; picrate, m.p. 145°, with neut. equiv. calcd. 414 and found by non-aqueous titration, 420. [c] An oil, isolated as the hydrochloride salt, for which the m.p. and analysis are given. [d] Described by H. L. Yale, E. J. Pribyl, W. Braker, F. H. Bergeim, and W. A. Lott, *J. Am. Chem. Soc.*, **72**, 3715 (1950). [e] Isolated as the monohydrate, for which the m.p. and analysis are given.

A related reaction was found to occur when styrene oxide was treated with phosgene.[2] In this case the secondary carbon atom, influenced by the electron-repelling phenyl group, is attacked. In both reactions addition of the chloride ion to the carbonium ion occurs where the electron cloud is least dense.



The apparent analogy between the reaction of phosgene with epoxides[2,3] and the reaction of thionyl chloride with β-hydroxyethylcarbamates bears a striking resemblance to earlier work with hydrohalides and epoxides. Tiffeneau first described the "reverse" addition of hydriodic acid to styrene

(2) J. I. Jones, *J. Chem. Soc.*, 2735 (1957). The chlorocarbamate (IV) was incorrectly described by Jones as 1-phenyl-1-carbamoxy-2-chloroethane, m.p. 71°C. It was derived from the reaction of styrene oxide with phosgene and subsequent treatment of the chloroformate ester with ammonia.

(3) L. K. Frevel and L. J. Kressley, U. S. Patents 2,820,809 and 2,820,810, Jan. 21, 1958, *Chem. Abstr.*, **52**, 11897c.

oxide[4] and similar additions to styrene oxide were studied by Golumbic and Cottle.[5]

Our findings appear to be in accord with the excellent discussion published by Kadesch[6] on his work with 3,4-epoxy-1-butene. Other related reactions of epoxides are described in the review by Winstein and Henderson.[7]

The effect of the substituent may best be illustrated by general equations. Where A is an electron -repelling group, B is an electron -attracting group and X is a halogen, these three sets of equations summarize the expected reactions:

$$\text{ACH(O)CH}_2 \xrightarrow{\text{HX}} \text{ACHXCH}_2\text{OH} \qquad (1a)$$

$$\text{BCH(O)CH}_2 \xrightarrow{\text{HX}} \text{BCHOHCH}_2\text{X} \qquad (1b)$$

$$\text{ACH(O)CH}_2 \xrightarrow{\text{COX}_2} \text{ACHXCH}_2\text{OCOX} \qquad (2a)$$

$$\text{BCH(O)CH}_2 \xrightarrow{\text{COX}_2} \text{BCH(OCOX)CH}_2\text{X} \qquad (2b)$$

$$\text{ACHCH}_2\text{OH} \xrightarrow{\text{SOCl}_2} \text{ACHClCH}_2\text{OCONH}_2 \quad (\text{OCONH}_2)$$

or $\text{ACHOHCH}_2\text{OCONH}_2$ (3a)

$$\text{BCHOHCH}_2\text{OCONH}_2 \xrightarrow{\text{SOCl}_2} \text{BCHCH}_2\text{Cl} \quad (\text{OCONH}_2) \qquad (3b)$$

or BCHCH_2OH (OCONH_2)

Structural Investigation. IV was also prepared by addition of HCl to styrene oxide and successive treatment with phosgene and ammonia. That this

$$\text{C}_6\text{H}_5\text{CH(O)CH}_2 \xrightarrow{\text{HCl}} \underset{\text{VI}}{\text{C}_6\text{H}_5\text{CHClCH}_2\text{OH}} \xrightarrow[\text{N(Et)}_3]{\text{COCl}_2} \text{C}_6\text{H}_5\text{CHClCH}_2\text{OCOCl} \xrightarrow{\text{NH}_3} \underset{\text{IV}}{\text{C}_6\text{H}_5\text{CHClCH}_2\text{OCONH}_2} \qquad (1)$$

is an "abnormal" addition to an epoxide was confirmed by the following independent synthesis of the structurally isomeric chlorocarbamate. 1-Phenyl-1-hydroxy-2-chloroethane (VII) was prepared by the reduction of phenacyl chloride.[8] VII was identified by its known *p*-nitrobenzoate[9] and converted to the carbamate (VIII) by stepwise treatment with phosgene and ammonia.

$$\text{C}_6\text{H}_5\text{COCH}_2\text{Cl} \xrightarrow{\text{Al(OCH(CH}_3)_2)_3} \underset{\text{VII}}{\text{C}_6\text{H}_5\text{CHOHCH}_2\text{Cl}} \xrightarrow[\text{N(Et)}_3]{\text{COCl}_2} \text{C}_6\text{H}_5\text{CH(OCOCl)CH}_2\text{Cl} \xrightarrow{\text{NH}_3} \underset{\text{VIII}}{\text{C}_6\text{H}_5\text{CH(OCONH}_2)\text{CH}_2\text{Cl}} \qquad (2)$$

The structure of IV was further confirmed by cyclization to 4-phenyl-2-oxazolidinone,[10] by a procedure which we soon hope to describe. By the same method, 1-(2-chlorophenoxy)-2-carbamoxy-3-chloropropane and 1-(2-methylphenoxy)-2-carbamoxy-3-chloropropane, respectively, were cyclized to known 5-substituted oxazolidinones.[11]

EXPERIMENTAL[12]

4-Phenyl-2-dioxolone (I). Styrene glycol (138 g., 1 mole) was stirred mechanically and heated in a 2-liter flask with 236 g. (2 moles) of diethyl carbonate and 2.8 g. of sodium methylate for approximately 2 hr. while distilling the alcohol which was formed through a short helices-packed column. When the still temperature had reached 124° the distillation had virtually ceased and the residue was treated with 6 g. of ammonium chloride. The excess ethyl carbonate was distilled *in vacuo* (10 mm.) with the final temperature of the still at 124°. A sample of the residue (I) was recrystallized twice from ethanol; m.p. 55.7–56.7°.

Anal.[13,14] Calcd. for $C_9H_8O_3$: C, 65.85; H, 4.91. Found: C, 65.11; H, 4.83.

1-Phenyl-1-carbamoxy-2-hydroxyethane (II) *and 1-phenyl-1-hydroxy-2-carbamoxy ethane* (III). The crude I, without isolation, was stirred overnight with 1000 ml. of isopropyl alcohol containing 40 g. of ammonia in a tightly stoppered flask. The nearly clear solution was heated to reflux to remove the excess ammonia and filtered hot after stirring with charcoal. The solvent was removed *in vacuo* on a steam bath to recover 190 g. of crude oily hydroxycarbamates. A 5 g. sample of the mixture was dissolved in 50 ml. of isopropyl acetate and chromatographed through a 15-inch column of active alumina. Two fractions, which crystallized on evaporation of the solvent, were recrystallized from isopropyl alcohol to obtain isomeric carbamates; m.p. 100° and 111°, respectively. The mixture melting point of these isomers was from 80–90°.

Using these crystals as seeds it was possible to fractionally crystallize the mixture from isopropyl alcohol to obtain sufficient material for further work.

Anal. Calcd. for $C_9H_{11}NO_3$: C, 59.65; H, 6.12; N, 7.73. Found II, m.p. 100.2–101.4°: C, 60.07; H, 5.94; N, 7.63. III, m.p. 111.6–112.6°: C, 60.34; H, 6.13; N, 7.97.

1-Phenyl-1-chloro-2-carbamoxyethane (IV). A. The crude mixture of hydroxycarbamates (18.1 g., 0.10 mole) was sus-

(4) M. Tiffeneau, *Ann. chim. phys.* [8] **10**, 322 (1907), *Chem. Abstr.*, **2**, 265.

(5) C. Golumbic and D. L. Cottle, *J. Am. Chem. Soc.*, **61**, 996 (1939).

(6) R. G. Kadesch, *J. Am. Chem. Soc.*, **68**, 41 (1946).

(7) S. Winstein and R. B. Henderson in *Heterocyclic Compounds*, R. C. Elderfield, editor, John Wiley and Sons, Inc., New York, 1950, Vol. I, pp. 1–60.

(8) T. Bergkvist, *Svensk Kem. Tid.*, **59**, 24 (1947), *Chem. Abstr.*, **41**, 5119h.

(9) W. E. Hanby and H. N. Rydon, *J. Chem. Soc.*, 114 (1946).

(10) M. S. Newman and W. M. Edwards, *J. Am. Chem. Soc.*, **76**, 1840 (1954).

(11) Y. M. Beasley, V. Petrow, O. Stephenson, and A. J. Thomas, *J. Pharm. and Pharmacol.*, **9**, 13 (1957).

(12) Melting points are corrected unless otherwise stated, boiling points are not.

(13) Microanalyses by Schwarzkopf Microanalytical Laboratory, Woodside, L. I., N. Y.

(14) Reported[2] 54–56°.

pended by stirring in 80 ml. of dry toluene and 13 g. (0.11 mole) of thionyl chloride was added at 30°. The evolution of hydrogen chloride was rapid at about 35°, and the mixture was slowly heated to 85°. It was then heated rapidly to 110°, and at reflux temperature for 2 hr. while passing in a slow stream of nitrogen to remove sulfur dioxide. The hot solution was then treated with charcoal and filtered. After concentrating to about 40 ml. and cooling, the crystallization was rapid. The total crude yield was 14.43 g., m.p. 67–71° (uncorrected). A sample of this was recrystallized twice from toluene-cyclohexane to obtain pure IV; m.p. 67.5–68.5°.

Anal. Calcd. for $C_9H_{10}ClNO_2$: C, 54.65; H, 5.01; N, 7.02; Cl, 17.76. Found: C, 54.36; H, 5.35; N, 7.01; Cl, 17.57.

B. A sample of IV was also prepared from 5 g. of styrene oxide according to the procedure of J. I. Jones[2] without purification of the intermediate chloroformate. On recrystallization of the crude product from toluene-cyclohexane, a yield of 4.29 g. (52.3%) of IV was obtained; m.p. 66.5–68°. This gave no depression in a mixture melting point with crystals from A.

C. Commercial styrene oxide (28 ml.) was added with cooling at 30–35° to 150 ml. of concentrated hydrochloric acid. The oil which separated was extracted with benzene, washed with water, dilute sodium carbonate, and finally with water. The solution was dried over sodium sulfate and, after removal of the solvent, was distilled at 110–114°/8 mm.; n_D^{29} = 1.5532. Only 11 g. of the crude chlorohydrin (VI) was obtained by this procedure, while the major portion remained as a polymer in the still.

The chlorohydrin (VI) (7.85 g., 0.05 mole) was added with 5.05 g. (0.05 mole) of triethylamine in 50 ml. of dry toluene to 5.45 g. (0.055 mole) of phosgene in 50 ml. of toluene while stirring at 5–7°. The mixture was then washed with ice water to remove triethylamine hydrochloride and added below 15° to 100 ml. of concentrated ammonium hydroxide with rapid stirring. After standing overnight at room temperature the toluene solution was evaporated *in vacuo* and the residue was recrystallized to obtain 2.5 g. of IV; m.p. 66–68°. A mixture melting point with material prepared by method A showed no depression. The low yield in this experiment may be accounted for by the relative ease with which IV is hydrolyzed.[2]

D. Samples of both II and III yielded IV on treatment with thionyl chloride as described in method A.

1-Phenyl-1-carbamoxy-2-chloroethane (VIII). Phenacyl chloride (15.5 g., 0.109 mole) was reduced in 100 ml. of isopropanol with aluminum powder (1.8 g.) and 0.1 g. mercuric chloride according to the procedure described by Bergkvist.[8] The yield of 1-phenyl-1-hydroxy-2-chloroethane (VII) was 11.5 g. (73%), b.p. 82–85°/0.5 mm., n_D^{20} 1.5480. This formed a *p*-nitrobenzoate,[9] m.p. 80–81°.

A sample of VII (7.84 g., 0.05 mole) with triethylamine (5.05 g., 0.05 mole) in 30 ml. of dry toluene was added at 3–7° with good stirring to phosgene (5.45 g., 0.055 mole) in 50 ml. of toluene. The amine salt was removed by washing with ice water and the toluene solution was added to 50 ml. of 28% ammonium hydroxide at 10–15°.

After stirring 1 hr. longer, the toluene was separated and washed with water. The solvent was distilled *in vacuo* and the residue was recrystallized from cyclohexane to recover 5.5 g. of crude VIII; m.p 83.5–84.5°. A sample recrystallized twice from cyclohexane-toluene yielded pure VIII; m.p. 84.2–84.8°.

Anal. Calcd. for $C_9H_{10}ClNO_2$: C, 54.65; H, 5.01; N, 7.02; Cl, 17.76. Found: C, 54.95; H, 5.09; N, 7.05; Cl, 17.56.

A mixture melting point of VIII with IV was 48.0–50.0°.

1-(2-Methoxyphenoxy)-2-carbamoxy-3-chloropropane. Although no yield data is given in Table I for the compounds described, the high yields which can be obtained are illustrated by the following three step synthesis.

The crude mixture of hydroxycarbamates, obtained from the stepwise treatment of 1-(2-methoxyphenoxy)-2,3-propanediol (99 g., 0.5 mole) with diethyl carbonate and ammonia,[1] was stirred in 400 ml. of toluene and 65 g. (0.55 mole) of thionyl chloride was added at room temperature. The mixture was heated slowly to 85° while passing in a slow stream of nitrogen and stirred 3 hr. longer at this temperature.

The mixture was cooled slowly, finally in an ice bath, and filtered. After washing with 50 ml. of benzene the 1-(2-methoxyphenoxy)-2-carbamoxy-2-chloropropane was dried to obtain 110 g. (85%) of virtually pure product, m.p. 105.0–106.0°.

1-(1-Piperidyl)-2-carbamoxy-3-chloropropane (IVD). IVD was prepared by a procedure analogous to that used in the three step synthesis of the 1-aryloxy-2-carbamoxy-3-chloropropanes already described. In the chlorination-rearrangement step excess thionyl chloride, however, was used as solvent for the reaction rather than toluene. The product was isolated by distillation of the excess thionyl chloride and treatment of the residue with aqueous sodium carbonate. The chlorocarbamate was extracted with chloroform, and the residual oil from evaporation of the solvent was recrystallized from isopropanol.

Acknowledgment. We are grateful to Dr. W. G. Bywater, S. B. Penick and Co., for reviewing this paper.

NUTLEY, N. J.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF FLORIDA]

Preparation of Some Unsaturated Sulfonium Halide-Mercuric Halide Double Salts[1]

GEORGE B. BUTLER AND GEORGE D. PRICE

Received February 2, 1959

Three unsaturated straight-chain alcohols were prepared, their double bonds being, respectively, two, three, and four carbon atoms removed from the carbinol carbon. The bromides of the respective alcohols were made; the physical constants of the hitherto unreported 5-hexen-1-ol and 1-bromohexene-5 were determined and they were characterized. The physical constants of the three new sulfides derived from the bromides were determined and these new compounds were characterized. Attempted syntheses of the three tris-sulfonium bromides were made. An attempt is made to explain the fact that the expected products were not obtained. Except for the tris(3-butenyl)sulfonium bromide–mercuric iodide, which could not be isolated, the eight new double salts of the tris(3-butenyl), -(4-pentenyl), and -(5-hexenyl) sulfonium bromides and, respectively, mercuric chloride, mercuric bromide, and mercuric iodide were made. Their physical states are reported and their respective constitutions were established by analysis. The effect of moving the double bond farther from the sulfur was an increase in the stability of the compound.

With a few exceptions, previous attempts to prepare unsaturated sulfonium salts have been unsuccessful. Steinkopf and Bessaritsch[2] prepared an addition compound of triallylsulfonium iodide and iodoform, but were unsuccessful in obtaining the free salt. Butler and Benjamin[3] were able to prepare methyldiallylsulfonium methyl sulfate and a number of unsaturated sulfonium halide–mercuric halide double salts, but were also unsuccessful in preparing triallylsulfonium iodide. Toennies and Kolb[4] were able to prepare acetyl methionineallylsulfonium bromide. Braun and Plate[5] reported preparing methylbis(1-cyclopentenyl)sulfonium iodide, but no analysis was given and the melting point of the product, crystallized from methyl alcohol, was identical with that of trimethylsulfonium iodide, 204°. Bost and Schultz[6] prepared diallyl -*p*-phenylphenacylsulfonium bromide by refluxing the reactants in absolute methyl alcohol. An attempt by Bloomfield[7] to prepare a sulfonium salt of dihydromyrcene tetrasulfide and methyl iodide yielded only trimethylsulfonium iodide. Lawson and Davson,[8] in their chlorination of mustard gas, reported some unsaturated sulfides and chlorosulfides whose sulfonium salts were unstable. Selker[9] reacted butylmethallyl sulfide and methyl iodide to produce dimethylbutylsulfonium iodide. From this they concluded that a double bond in the position α to a sulfur is unstable to methyl iodide.

The difficulty in preparing any sulfonium salt containing groups larger than methyl lies in the fact that the groups are subject to displacement by smaller groups. The smaller group might come from the solvent[3] or from the dissociation and subsequent recombination of the sulfonium salt, the larger groups having been eliminated in the interim. Cahours[10] obtained trimethyl sulfonium iodide from the reaction of benzyl bromide and methyl sulfide; Krüger[11] was able to change triethylsulfonium iodide to the trimethyl derivative by heating the former with excess methyl iodide at 150°. Masson,[12] in attempts to prepare a disulfonium salt from ethylene bromide and an alkyl sulfide obtained only trimethylsulfonium iodide. Platanov[13] and Anisimov reacted ethyl and methyl iodide with monothioparaldehyde, dithioparaldehyde, and ethyl monothioacetate, obtaining in every case the triethyl - or trimethylsulfonium iodide.

Ray and Levine[14] explained these apparently unrelated anomalies by postulating the dissociation of the sulfonium salt first formed with a subsequent recombination to give a sulfonium salt containing the smallest possible radicals. An apparent exception to this mechanism is shown by the work of P. C. Ray[15] who reacted methyl mercaptan with mercuric nitrite to form methyl mercury mercaptide nitrite. Subsequent reaction of this compound with butyl iodide gave a disulfide containing not one but two butyl groups, indicating the displacement of a lighter by a heavier radical. From this,

(1) Taken from a thesis presented by G. D. Price to the Graduate Council of the University of Florida in partial fulfillment of the requirements for the degree of Master of Science.

(2) W. Steinkopf and R. Bessaritsch, *J. prakt. Chem.*, **109**, 230 (1925).

(3) G. B. Butler and B. M. Benjamin, *J. Am. Chem. Soc.*, **74**, 1846 (1952).

(4) G. Toennies and J. J. Kolb, *J. Am. Chem. Soc.*, **67**, 1141 (1945).

(5) J. V. Braun and T. Plate, *Ber.*, **67**, 281 (1934).

(6) R. W. Bost and H. C. Schultz, *J. Am. Chem. Soc.*, **64**, 1165 (1942).

(7) G. F. Bloomfield, *J. Soc. Chem. Ind.*, **67**, 14 (1948).

(8) W. E. Lawson and T. P. Davson, *J. Am. Chem. Soc.*, **49**, 3119 (1927).

(9) M. L. Selker, *Ind. Eng. Chem.*, **40**, 1467 (1948).

(10) A. Cahours, *Compt. rend.*, **80**, 1317 (1875).

(11) F. Krüger, *J. prakt. Chem.*, [2] **14**, 193 (1877).

(12) O. Masson, *J. Chem. Soc.*, 233 (1886).

(13) M. S. Platanov and S. B. Anisimov, *J. Gen. Chem. (U.S.S.R.)*, **5**, 622 (1935).

(14) F. E. Ray and I. Levine, *J. Org. Chem.*, **2**, 267 (1937).

(15) P. C. Ray, *J. Chem. Soc.*, 603 (1916).

it is readily apparent then, that preparation of all but the simplest of sulfonium salts is very difficult.

Contrarily, double salts of the sulfonium halides and mercuric halides form with extraordinary speed and facility. Smiles[16] found the reaction at room temperature of ethyl iodide and methyl sulfide to be incomplete at the end of 3 days. Addition of mercuric iodide caused the reaction to be quantitatively complete in 15 min. In addition, they noted that the time element involved in rearrangement of the double salts was such as to allow preparation of mixed alkyl radical sulfonium halide–mercuric halide compounds.

There is still a lack of knowledge as to why the sulfonium halide-mercuric halides are formed with such ease. That they are ionic is shown by conductivity measurements, boiling point elevations, and parachor measurements. Cavell and Sugden[17] state that the structure $[R_3S]^+[HgI_3]^-$ is the most probable in view of the fact that silver iodide is readily soluble in the sulfonium iodides, probably with the formation of the more stable $[HgI_4]^=$ ion. Their statement that the sulfur is quadrivalent is borne out by the experiments of Ray and Adhikary.[18]

The ease of formation of a sulfonium bromide–mercuric bromide double salt is probably due to the abstraction by the mercuric bromide of the alkyl bromide bromine atom to form the $HgBr_3^-$ ion. The alkyl carbonium ion thereby formed is likely to attack an electron pair of the sulfur of the thioether. The reaction would be reversible only to the extent of the dissociation of the $HgBr_3^-$ ion to reform free bromide ion and mercuric bromide. The work of Cavell and Sugden[17] supports this hypothesis. That the $HgBr_3^-$ ion does dissociate is shown by the work of Smiles.

Attempts have been made in this laboratory to prepare unsaturated sulfonium halides preparatory to polymerizing them to form sulfonium ion exchange resins. That such attempts were unsuccessful is understandable in view of the failures of other workers to prepare even the simpler saturated sulfonium halides, probably because of the failure of the reaction, rearrangement of the groups present in the intermediate, or transalkylation by the solvent.

The attempts were carried out in sealed thick-wall glass tubes, both with and without solvents. Temperatures varying from 100° to 300° were used. The one case in which a reaction occurred was unsuccessful in that trimethyl sulfonium iodide was obtained and not the desired product.

Because of the instability of the triallyl sulfonium halide–mercuric halide double salts,[3] it was decided to prepare unsaturated sulfonium halide–mercuric halide double salts with the double bonds farther removed from the sulfur atom, in an attempt to correlate this distance with the instability of the salt. It was thought that a greater distance between the double bond and the sulfur atom would effect a behavior more nearly similar to the saturated analogs of the unsaturated salts chosen. For this reason, the mercuric chlorides, bromides, and iodides of the tris(3-butenyl), tris(4-pentenyl), and tris(5-hexenyl) sulfonium bromides were prepared.

Strömholm[19] was able to prepare sulfonium chloride–mercuric chloride double salts in which the ratios of sulfonium chloride to mercuric chloride were 2:1, 1:1, 1:2, 1:3, and 1:6, by varying the proportions of sulfonium chloride to mercuric chloride and by using different solvents. He states that the 1:1 ratio double salt is always obtained when the reaction is run in ether, and, further, that repeated ether washings of the higher salts (higher ratio of mercuric chloride to sulfonium chloride) remove mercuric chloride with the ultimate production of a 1:1 double salt. Smiles[20] found that the reaction to form dimethylethylsulfonium iodide–mercuric iodide was essentially complete in 2 min.; whereas 3 days were necessary to effect an incomplete reaction between dimethyl sulfide and ethyl iodide to give a highly impure product. His observation[21] that rearrangement occurs in the double salts is rendered unimportant by the fact that only tris-sulfonium halide–mercuric halide double salts were prepared in the present study.

Numerous other references to the preparation of sulfonium halide double salts using, to replace the mercuric halides, the halides[22] (to give polyhalides), antimony halides,[23] and the haloforms[24,2] are found in the literature. It is not clear what type of bonding is generally present, though if, as Cavell and Sugden[17] believe, the salts–mercuric halide salts are in the form $[R_3S]^+[HgI_3]^-$, it would seem possible to exchange the HgI_3^- ion for some other ion by passing a solution of the salt over the proper ion exchange resin, and thus indirectly arrive at the desired unsaturated sulfonium salt.

References to purification of the double salts[3,25] generally apply only to definite liquids or solids, not to exceedingly viscous oils. The solids need only be recrystallized from the proper solvent, while the liquids can be washed free of impurities, the reactants being quite soluble in ether. Attempts to purify the sulfonium halide–mercuric halide double

(16) T. P. Hilditch and S. Smiles, *J. Chem. Soc.*, 1394 (1907).

(17) H. J. Cavell and S. Sugden, *J. Chem. Soc.*, 2572 (1930).

(18) P. C. Ray and N. Adhikary, *J. Indian Chem. Soc.*, 1, 297 (1930).

(19) D. Strömholm, *Ber.*, **32**, 2892 (1899).

(20) S. Smiles, *J. Chem. Soc.*, **87**, 450 (1905).

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salts prepared below by 25 washings of each salt with 20-ml. portions of dry ether failed completely. It was finally decided to dissolve the oils in some solvent, then to precipitate them by the addition of dry ether. Solvents tried were *n*-hexane, methyl isobutyl ketone, diisobutyl ketone, acetone, diethyl ketone, methyl ethyl ketone, methyl isopropyl ketone, diisopropyl ketone, *n*-butyl ethyl ketone, methyl *n*-amyl ketone, dioxane, and dibenzyl ketone. Diisopropyl ketone was used for five of the eight double salts; solvents (which would give up the salts upon addition of dry ethyl ether) were not found for the other three. For those salts insoluble in diisopropyl ketone, another procedure was adopted. They were alternately washed with ether, and heated on a steam bath.

The effect of moving the double bond farther from the sulfur atom appears to have a stabilizing influence on the molecule. The severe treatment (heating them to 100° in purification attempts) did not decompose the salts for which solvents were not found, in sharp contrast to the salts of Butler and Benjamin,[2] which salts were unstable at room temperature.

As intermediates, 3-buten-1-ol, 4-penten-1-ol, 5-hexen-1-ol, the corresponding bromides, and the corresponding sulfides were prepared. The 3-buten-1-ol was made by the method of Pariselle,[26] as modified by Linstead and Rydon.[27] The 4-penten-1-ol and 5-hexen-1-ol were made[28] from tetrahydrofurfuryl alcohol and tetrahydro-pyran-2-methanol, respectively. The bromides were made by the addition of phosphorus tribromide to the respective alcohols.[29] The sulfides were made by the addition of a water solution of reagent grade sodium sulfide to the bromide, dissolved in alcohol.[30] Preparation of the sulfonium halide–mercuric halide double salts followed the procedure of Butler and Benjamin.[3]

EXPERIMENTAL

3-Buten-1-ol. Allyl bromide was added dropwise to a mixture of dry ether, magnesium shavings, and dry trioxymethylene, according to the procedure of Pariselle,[26] as modified by Linstead and Rydon.[27] Considerable difficulty was experienced in drying the trioxymethylene. The course finally taken was to heat the required amounts of magnesium shavings and trioxymethylene in the reaction flask while vigorously stirring and passing in a slow stream of air previously passed through Drierite. B.p. 112–114°. Yield 24.6%; n_D^{25} 1.4199; reported n_D^{25} 1.4189.

4-Penten-1-ol. This alcohol was prepared from tetrahydrofurfuryl alcohol by the procedure of Brooks and Snyder.[28]

5-Hexen-1-ol. To 860 g. (7.5 moles) of tetrahydropyran-2-methanol and 652 g. (8.25 moles) of pyridine contained in a 3-liter, three-necked, standard-taper flask equipped with stirrer, reflux condenser, addition funnel, and thermometer, and cooled in an ice bath, was added 940 g. (7.90 moles) of thionyl chloride at a rate such as to keep the reaction temperature below 60°. When the addition was complete, the mixture was stirred 4 hr. without the ice bath. Sufficient water to dissolve the pyridine hydrochloride was added, after which the mixture was extracted with eight 500 ml. portions of ether. Distillation of the ether left a residue which was dried over anhydrous magnesium sulfate. Distillation at 22–23 mm. gave 435.5 g. (43.1% yield) of tetrahydropyran-2-methyl chloride.

The chloride, dissolved in 1.5 l. of dry ether, was then added dropwise to 181.2 g. (7.88 moles) of sodium, covered with 1.0 l. of dry ether, and contained in a 3-liter, three-neck, standard-taper flask equipped as above except that a calcium chloride drying tube was fitted into the condenser. Upon completion of the reaction, the mixture was stirred for an additional 2 hr. without the ice bath, decanted into 2 l. of ice water, separated, dried over anhydrous magnesium sulfate, and distilled. The yield of 5-hexen-1-ol was 191.0 g. (25.5% yield) of material boiling at 71–73° at a pressure of 21 mm., n_D^{25} 1.4360.

Anal. Calcd. for $C_6H_{12}O$: C, 71.92; H, 11.07. Found: C, 72.01; H, 11.43.

1-Bromo-3-butene. To 70.8 g. (0.982 mole) of 3-buten-1-ol contained in a three-neck, 300-ml., standard-taper flask equipped with stirrer, addition funnel, thermometer, and reflux condenser and cooled in an ice-salt mixture, was added dropwise to 89.1 g. (0.330 mole) of phosphorus tribromide at such a rate as not to allow the reaction temperature to exceed 0°. Addition complete, the mixture was stirred and allowed to reach 20° over a period of 2 hr., left to stand overnight, and steam distilled. The lower layer of the distillate was separated, washed with 10% sodium carbonate solution, dried over Drierite, and fractionally distilled, yielding 42.5 g. (32.1%) of the product, boiling at 96–98° and having a refractive index, n_D^{25} 1.4595. The reported boiling point is 98.5–99° at 758 mm., the refractive index n_D^{20} 1.4621.[31]

1-Bromopentene-4. The bromination of 4-penten-1-ol was carried out in an exactly similar manner to that of 3-buten-1-ol. To 86.2 g. (1.0 mole) of 4-penten-1-ol was added 99.1 g. (0.336 mole) of phosphorus tribromide, giving, after final purification, 47.2 g. (31.6% yield) of 1-bromopentene-4, having a boiling point range of 51–53° at 52–53 mm. and a refractive index n_D^{25} 1.4651. Kharasch and Fuchs[32] state that the boiling point is 125–126°, the refractive index n_D^{20} 1.4632.

1-Bromohexane-5. Bromination of 247 g. (2.47 moles) 5-hexen-1-ol with 270.8 g. (1.0 mole) of phosphorus tribromide in the above manner gave 151.1 g. (37.5% yield) of the bromide boiling at 76–78° at a pressure of 4–5 mm., and having a refractive index of n_D^{25} 1.4630.

Anal. Calcd. for $C_6H_{11}Br$: C, 44.18; H, 6.80; Br, 49.00. Found: C, 44.31; H, 7.10; Br, 48.38.

Bis(3-butenyl) sulfide. To 10.0 g. (0.074 mole) of 1-bromo-3-butene dissolved in 30 ml. of 95% ethanol contained in a 300-ml. three-neck flask equipped with stirrer, addition funnel, and reflux condenser, and heated on a steam bath was added dropwise 8.9 g. (0.037 mole) of sodium sulfide nonahydrate. Stirring, while at reflux, was continued for 8 hr. after addition. When the refluxing was completed, the mixture was added to 50 ml. of 25% sodium chloride solution, the upper, oily layer separated and dried over Drierite, and five 20-ml. extracts of the sodium chloride solution with *n*-hexane were added. The hexane solution of the sulfide, after overnight drying, was distilled at atmospheric pressure until the pot temperature read 180°, at which point distillation was continued at 17 mm., giving 2.32 g. (43.3%

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(27) R. P. Linstead and H. M. Rydon, *J. Chem. Soc.*, 1998 (1934).

(28) L. A. Brooks and H. R. Snyder, *Org. Syntheses*, 25, 84 (1945).

(29) D. A. Shirley, *Preparation of Organic Intermediates*, John Wiley & Sons Inc., New York, 1951, p. 94.

(30) Ref. 29, p. 32.

(31) A. Juvala, *Ber.*, 63, 1992 (1930).

(32) M. S. Kharasch and C. F. Fuchs, *J. Org. Chem.*, 9, 368–70 (1944).

yield) of material boiling at 78–80°, and having a refractive index, n_D^{25} 1.4825.

Anal. Calcd. for $C_8H_{14}S$: C, 67.57; H, 9.92. Found: C, 67.65; H, 10.03.

Bis(4-pentenyl) sulfide. Preparation of the sulfide in the above manner from 78.4 g. (0.526 mole) of the bromide, 150 ml. of 95% ethyl alcohol, 125 ml. of water, and 65.5 g. (0.273 mole) of sodium sulfide nonahydrate gave 19.8 g. (22.1% yield) of the product, boiling at 100–102° at 11–12 mm. pressure, and having a refractive index, n_D^{25} 1.4806.

Anal. Calcd. for $C_{10}H_{18}S$: C, 70.52; H, 10.65; S, 18.83. Found: C, 69.79; H, 10.32; S, 19.21.

Bis(5-hexenyl) sulfide. Preparation of the sulfide in the above manner from 50 g. (0.307 mole) of 1-bromo-5-hexene, 100 ml. of 95% ethanol, 37.2 g. (0.155 mole) of sodium sulfide nonahydrate, and 42 ml. of water gave 20.12 g. (66.0% yield) of the sulfide, boiling at 98–100.5°, at 4–5 mm. pressure and having a refractive index n_D^{25} 1.4782.

Anal. Calcd. for $C_{12}H_{22}S$: C, 72.63; H, 11.18; S, 16.16. Found: C, 72.88; H, 11.25; S, 15.71.

Attempted preparation of tris(3-butenyl)sulfonium bromide. In a heavy-walled glass tube were sealed 0.945 g. (0.007 mole) of 1-bromo-3-butene, and 0.994 g. (0.007 mole) of bis(3-butenyl) sulfide. The tube was enclosed in a heavy wire mesh in order to minimize the effects of a chance explosion and heated to 100° for 24 hr. Upon cooling the tube in an ice–salt bath there was no precipitation. After 24 hr. exposure at 200° no apparent reaction had occurred. To make certain that no reaction had occurred, the tube was immersed in a Dry Ice–acetone mixture and opened. Addition of ether did not cause precipitation.

Attempted preparation of tris(4-pentenyl)sulfonium bromide. In a heavy-walled glass tube were sealed 1.49 g. (0.01 mole) of 1-bromopentene-4 and 1.70 g. (0.01 mole) of bis(4-pentenyl) sulfide. After 48 hr. at 100° no precipitation was apparent upon placing the tube in an ice-salt bath. The tube was then heated at 200° for 48 hr. and was placed in a Dry Ice–acetone mixture before opening; addition of ether to the contents did not cause any precipitation.

Attempted preparation of bis(4-pentenyl)methylsulfonium iodide. In a heavy-walled glass tube was sealed 1.70 g. (0.01 mole) of bis(4-pentenyl) sulfide, methyl iodide, and 1.00 g. (0.01 mole) of 5-hexen-1-ol. The tube was heated at 100° for 48 hr., cooled in a Dry Ice–acetone bath, opened, and dry ether was added. The precipitate which formed was recrystallized from acetone. The crystals melted at 202–204°, the melting point of trimethyl sulfonium iodide.

Attempted preparation of tris(5-hexenyl)sulfonium bromide. In a heavy-walled glass tube was sealed 1.98 g. (0.01 mole) of bis(5-hexenyl) sulfide and 1.63 g. (0.01 mole) of 1-bromohexene-5. The tube was heated for 12 hr. at 300°. After cooling in a Dry Ice–acetone mixture, the tube was opened and dry ether added. No precipitation was apparent; the contents did not appear to be decomposed by the treatment.

Preparation of the double salts of tris(3-butenyl)sulfonium bromide with mercuric chloride, mercuric bromide, and mercuric iodide. To each of three 20 × 150 mm. test tubes were added 0.945 g. (0.007 mole) of 1-bromo-3-butene, 0.994 g. (0.007 mole) of bis(3-butenyl) sulfide, and 20 ml. of acetone. To the first tube was added 1.90 g. (0.007 mole) of mercuric chloride, to the second 2.52 g. (0.007 mole) of mercuric bromide, and to the third 3.18 g. (0.007 mole) of mercuric iodide. Because the mercuric iodide would not dissolve in the case of the third reaction, gentle reflux was maintained for 1 hr. in an effort to force solution. (It was necessary to decant the liquid from the undissolved mercuric iodide into another test tube before evaporation.) Subsequently, the acetone was evaporated from the tubes in a vacuum desiccator and the contents washed with ether. No product was obtained from the tube containing mercuric iodide. Attempts to find solvents for the reactions involving mercuric chloride and mercuric bromide failed; it was therefore necessary to adopt the method outlined in the general procedure. Each salt was alternately melted on the steam bath and washed ten times with dry ether. The two salts were obtained finally in the form of grey gums.

Anal. Calcd. for $C_{12}H_{21}SBr.3HgCl_2$: C, 13.22; H, 1.94. Found: C, 12.72; H, 2.00. Calcd. for $C_{12}H_{21}SBr.2HgBr_2$: C, 14.40; H, 2.12. Found: C, 13.50; H, 2.18.

Preparation of the double salts of tris(4-pentenyl)sulfonium bromide with mercuric chloride, mercuric bromide, and mercuric iodide. To each of three 20 × 150 mm. test tubes were added 1.49 g. (0.01 mole) of 1-bromo-4-pentene, 1.70 g. (0.01 mole) of bis(4-pentenyl) sulfide, and 20 ml. of acetone. To the first tube was added 2.71 g. (0.01 mole) of mercuric chloride, to the second 3.60 g. (0.01 mole) of mercuric bromide, and to the third, 4.54 g. (0.01 mole) of mercuric iodide. Again, the tube containing iodide was gently refluxed for 1 hr. in an attempt to force the reaction, and decanted into another test tube before evaporation. Subsequently, the acetone was evaporated from the tubes in a vacuum desiccator and the contents washed with ether. The contents of the tube to which the mercuric chloride had been added were ether insoluble in the solvents tried, or too soluble, so as to be difficult to precipitate out. Therefore, they were melted and washed with dry ether alternately ten times. The effect of the attempted purification is shown in the analyses. The contents of the tubes containing the mercuric bromide and the mercuric iodide were soluble in isopropyl ketone and were therefore dissolved in the minimum amount thereof and precipitated with dry ether. This was repeated five times. The mercuric chloride double salt was a very viscous, yellow oil, the mercuric bromide double salt a dark red oil, and the mercuric iodide double salt an orange oil.

Anal. Calcd. for $C_{15}H_{27}SBr.3HgCl_2$: C, 16.77; H, 2.38. Found: C, 16.73; H, 2.72. Calcd. for $C_{15}H_{27}SBr.HgBr_2$: C, 26.50; H, 4.00. Found: C, 25.85; H, 4.17. Calcd. for $C_{15}H_{27}SBr.HgI_2$: C, 23.28; H, 3.52. Found: C, 23.30; H, 3.51.

Preparation of the double salts of tris(5-hexenyl)sulfonium bromide and mercuric chloride, mercuric bromide, and mercuric iodide. To each of three test tubes was added 1.63 g. (0.01 mole) of 1-bromo-5-hexene, 1.98 g. (0.01 mole) of bis(5-hexenyl) sulfide, and 20 ml. of acetone. To the first tube was added 2.71 g. (0.01 mole) of mercuric chloride, to the second 3.60 g. (0.01 mole) of mercuric bromide, and to the third 4.54 g. (0.01 mole) of mercuric iodide. Reflux of the tube containing mercuric iodide was again carried out for 1 hr. After decanting the liquid from the mercuric iodide into another test tube, evaporation of the acetone was carried out in a vacuum desiccator. When evaporation was complete, the contents of the tubes were washed with ether and purified by alternately dissolving the contents in diisopropyl ketone and precipitating with dry ether. This cycle was repeated five times. As finally purified, both the mercuric chloride and the mercuric bromide double salts were light brown in color; the mercuric iodide double salt was pale yellow.

Anal. Calcd. for $C_{18}H_{33}SBr.HgCl_2$: C, 34.15; H, 5.26. Found: C, 34.70; H, 5.22. Calcd. for $C_{18}H_{33}SBr.HgBr_2$: C, 29.95; H, 4.61. Found: C, 29.65; H, 4.79. Calcd. for $C_{18}H_{33}SBr.HgI_2$: C, 26.50; H, 4.08. Found: C, 26.30; H, 4.15.

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[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, THE HEBREW UNIVERSITY]

Syntheses of *N*-Alkyl-aspartic Acids and N^2-Alkyl-α-asparagines

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Received February 6, 1959

General methods for the preparation of *N*-alkyl-aspartic acids and N^2-alkyl-α-asparagines *via* maleic anhydride were worked out. The former were obtained on alkaline hydrolysis of their β-methyl esters, obtained by addition of amines to monomethyl maleate. Reaction of ammonia with the anhydride hydrochlorides of *N*-alkyl-aspartic acids or with their mixed anhydrides with chloroformic acid (obtained on reaction with phosgene) gave N^2-alkyl-α-asparagines.

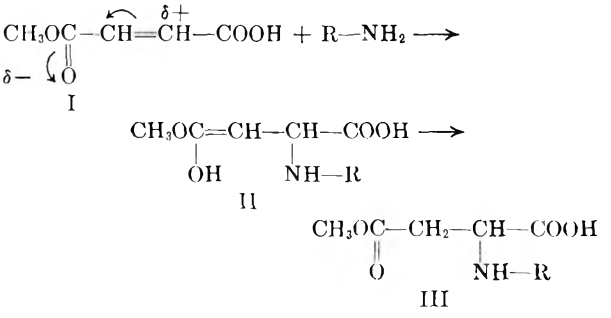
Only a few *N*-alkyl-aspartic acids are reported in the literature. They were obtained in very small yields by the action of amines on halo succinic acids,[1] or by alkylation of aspartic acid with aldehydes.[2] In a patent[3] a general method for their preparation was described; however, no melting points, analyses etc., were given. It consists of heating for a long time, maleic anhydride in aqueous solution with a large excess of amine in an autoclave. The amide of the *N*-alkyl-aspartic acid thus formed is hydrolyzed by very long refluxing with concentrated sodium hydroxide. Separation of the *N*-alkyl-aspartic acids — many of which are soluble in water — from the large amounts of salts formed, is very difficult.

A simple preparation of *N*-benzylaspartic acid had been reported recently[4] by the reaction of benzylamine with aqueous maleic acid under reflux. However, this method did not prove a general one[5] and the reaction of other amines with maleic acid either in aqueous solution or otherwise did not give the required *N*-alkyl-aspartic acid but led to the formation of amine salts of maleic acid or to unidentified products.

In continuation of this work, we found that increasing the activity of the double bond of maleic acid by the introduction of an ester group enabled a smooth nucleophilic addition of amines to the double bond. Reaction of monomethyl maleate, prepared easily from maleic anhydride and methanol, with one equivalent of amine led only to opening of the double bond, giving *N*-alkylaspartic acid β-methyl esters, without attacking the ester group; showing that addition to the double bond is preferable to amidation. Use of two equivalents of amine led both to addition to the double bond and amidation giving N^2-alkyl-*N*-alkyl-β-asparagines. These reactions can be carried out in methanol, dioxan, or best in pyridine. The structure of the β-methyl esters was further proved by their positive reaction with copper carbonate as is compatible with their having a free α-carboxyl group.[6]

The addition reaction proceeds probably by the following mechanism (Chart I). The ester group, being more electronegative than the carboxyl group, polarizes the double bond as shown in I and the nucleophilic amine attaches to the positive carbon atom by the unshared electron pair of the nitrogen. 1,4- addition of the amine gives the enolic form (II) which passes over to the *N*-alkyl-aspartic acid β-methyl ester (III).

CHART I



The *N*-alkyl-aspartic acids were obtained from the corresponding β-methyl esters which, contrary to the amides, are easily hydrolyzed by cold dilute alkali. Since many of the *N*-alkyl-aspartic acids are soluble in water, and thus difficult to purify them from soluble inorganic salts, hydrolysis of the β-methyl esters was carried out with barium hydroxide. Addition of an equivalent of sulfuric acid precipitated the barium as sulfate. Evaporation of the filtrate gave the *N*-alkyl-aspartic acids in almost quantitative yield. Complete hydrolysis of the ester groups was proved by negative methoxyl determinations.

No general method had been given for the preparation of N^2-alkyl-α-asparagines. A difficult procedure for the preparation of N^2-methyl-α-asparagine had been reported.[7] Their preparation was carried out either by action of dry ammonia on the α-mixed anhydrides of the *N*-alkyl-aspartic acids

(1) O. Lutz, *Ber.*, **67**, 648 (1934).

(2) S. Kano, *J. Pharm. Soc., Japan*, **66**, 4 (1946).

(3) W. Reppe and H. Ufer, U. S. Patent **2,200,220** (1940); *cf.* I. G. Farbenind, French Patent **793,504** (1936).

(4) M. Frankel, Y. Liwschitz, and Y. Amiel, *J. Am. Chem. Soc.*, **75**, 330 (1953).

(5) Y. Liwschitz and R. D. Irsay, private communication.

(6) P. Desnuelle and G. Bonjour, *Biochim. et Biophys. Acta*, **9**, 356 (1952); *cf.* also ref. 8.

(7) G. Körner and A. Menozzi, *Gazz. chim. ital.*, **19**, 427 (1889); Beilstein, *Organische Chemie* **IV**, 485.

TABLE I

PREPARATION OF *N*-ALKYL-DL-ASPARTIC ACIDS β-METHYL ESTERS

Substance, *N*-Alkyl-Aspartic Acid β-Methyl Ester	Yield, %	M.P., °C.	Formula	Carbon, %		Hydrogen, %		Nitrogen, %	
				Calcd.	Found	Calcd.	Found	Calcd.	Found
Cyclohexyl-	55[a]	216	$C_{11}H_{19}NO_4$	57.7	57.9	8.3	8.3	6.1	6.1
n-Hexyl-	69	213	$C_{11}H_{21}NO_4$	57.1	57.5	9.1	9.1	6.1	5.9
n-Butyl-	68	220	$C_9H_{17}NO_4$	53.2	53.1	8.4	8.2	6.9	6.7
Allyl-	66	213	$C_8H_{13}NO_4$	51.3	51.9	7.0	7.2	7.5	7.2
Isobutyl-[b]	85	215	$C_9H_{17}NO_4$	53.2	53.4	8.4	8.5	6.9	7.1
Benzyl-[c]	65	219	$C_{12}H_{15}NO_4$	60.8	60.8	6.4	6.6	5.9	5.8
Methyl-[d]	57	206	$C_6H_{11}NO_4$					8.7	9.0

[a] Reaction carried out in dioxan. [b] Using 2 equivalents of isobutylamine gave N^2-isobutyl-*N*-isobutyl-DL-β-asparagine, crystallized from water, m.p. 238°. *Anal.* Calcd. for $C_{12}H_{24}N_2O_3$: C, 59.0; H, 9.8; N, 11.5. Found: C, 59.4; H, 9.8; N, 11.3. [c] Using 2 equivalents of benzylamine gave N^2-benzyl-*N*-benzyl-β-DL-asparagine, crystallized from water, m.p. 216°. Identical with substance prepared by different method (cf. ref. 4). [d] Methylamine 33% alcoholic solution was used, and this added to the pyridine solution of the monomethyl maleate.

with chloroformic acid, obtained by reaction of phosgene with the *N*-alkyl-aspartic acids[8,9]; or by the action of aqueous ammonia on the *N*-alkyl-aspartic anhydride hydrochlorides formed in the cold by elimination of water from *N*-alkyl-aspartic acids by a (1:1) mixture of acetyl chloride–acetic acid.[10] The first method is to be preferred as it gave purer compounds. Considering the similar solubilities of the N^2-alkyl-α-asparagines and ammonium chloride we found that the most efficient method of purification was by cation exchange resins.[11]

The N^2-alkyl-α-asparagines are soluble in water and in hot ethanol, and insoluble in acetone. They give a positive sensitive red biuret reaction; and a negative reaction with copper carbonate when this is added to their boiling aqueous solutions[6] contrary to their β-isomers.[9] Having no α-carboxyl group available for zwitterion formation with the α-amino group, they have lower melting points than the β-isomers reported.[9]

EXPERIMENTAL[12]

Preparation of N-alkyl-aspartic acids β-methyl esters. Maleic anhydride (0.054 mole) was dissolved in 15 ml. absolute methanol and refluxed for 30 min., excess methanol distilled *in vacuo*. The monomethyl maleate thus obtained was cooled in ice water, 10 ml. pyridine followed by 0.05 mole of amine added, and refluxed at 110–120° (oil bath) for about 1 hr. The reaction mixture assumed a brownish red color and the reaction product generally started to precipitate within 15 min. It was purified by trituration with acetone or ether-acetone (1:1), to remove the color of the mother pyridine solution, and filtered.

The esters were generally crystallized from a minimum volume of hot water, and acetone added to complete precipitation. The white crystalline material thus obtained gave negative reaction with aqueous potassium permanganate indicating the absence of double bonds.

The *N*-alkyl-aspartic acids β-methyl esters thus prepared are listed in Table I.

Preparation of N-alkyl-aspartic acids. *N*-Alkyl-aspartic acid β-methyl ester (0.05 mole) was dissolved in 0.125 mole barium hydroxide solution (0.35*N*) and left for 2 hr. at room temperature. The solution was heated for 10 min. near the boiling point and an exact equivalent of hot sulfuric acid (1*N*) was added portionwise with shaking to get an easily filtrable precipitate of barium sulfate. The solution was filtered through a sintered-glass Büchner funnel with fine perforations and evaporated to dryness *in vacuo* from a water bath. The *N*-alkyl-aspartic acid, which usually crystallized, was triturated with acetone and filtered. Recrystallization was carried out from a minimum volume of hot ethanol-water (2:1), more ethanol was then added to complete precipitation.

The *N*-alkyl-aspartic acids thus prepared are listed in Table II.

Preparation of N^2-alkyl-α-asparagines. Method I. Dry *N*-alkyl-aspartic acid (2 g.) was suspended in 100 ml. dry dioxan in a 3-necked flask equipped with a gas leading tube, reflux condenser connected to a calcium chloride tube, and a mechanical stirrer. Phosgene, dried over concentrated sulfuric acid, was bubbled in with stirring for 1 hr. and the temperature maintained at 60°. The substance usually dissolved within the first 15 min. Excess phosgene was removed *in vacuo* at 30°. The solution of the mixed anhydride with chloroformic acid thus obtained was transferred to a 3-necked flask equipped with a gas leading tube and a mechanical stirrer, and dry ammonia gas passed in with stirring and cooling for 15 min. The sticky precipitate formed was separated from the dioxan by decantation and dissolved in water. The solution was evaporated to dryness on a water bath to remove excess ammonia and the residue dissolved again in water. To remove the ammonium chloride the solution was passed through a column packed with (about 2.5–3 equivalents) cation exchange resin (nuclear sulfonic acid type resin, Amberlite IR-120). The course of the absorption and desorption of the N^2-alkyl-α-asparagines was followed conveniently by their sensitive reaction with biuret reagent. The ammonium ions and the N^2-alkyl-α-asparagine were held on the column while the chloride ions were removed as hydrochloric acid. The column was washed with water till the effluent liquid gave a negative reaction with silver nitrate. The column was eluted with ammonia (4–5%) till the eluent gave a negative red biuret reaction. The N^2-alkyl-α-asparagine, which crystallized on evaporation to

(8) Y. Liwschitz and A. Zilkha, *J. Am. Chem. Soc.*, **76**, 3698 (1954).

(9) Y. Liwschitz, Y. Edlitz-Pfeffermann, and Y. Lapidoth, *J. Am. Chem. Soc.*, **78**, 3069 (1956).

(10) A. Zilkha and Y. Liwschitz, *J. Chem. Soc.*, 4397 (*1957*).

(11) E. I. Vasilyeva and R. Kh. Freidlina, *Bull. Acad. Sci., U.S.S.R., Div. Chem. Sci.* (*English Translation*), **2**, 169 (1956).

(12) Microcombustion analyses were carried out by Drs. Weiler and Strauss. Melting points were determined in a Fisher-Johns apparatus.

TABLE II

PREPARATION OF *N*-ALKYL-DL-ASPARTIC ACIDS

Substance *N*-Alkyl-Aspartic Acid[a]	M.P., °C.	Formula	Carbon, %		Hydrogen, %		Nitrogen, %	
			Calcd.	Found	Calcd.	Found	Calcd.	Found
Cyclohexyl-	216	$C_{10}H_{17}NO_4$	55.8	55.8	8.0	8.0	6.5	6.5
n-Hexyl-[b]	168	$C_{10}H_{19}NO_4$	55.3	55.5	8.7	8.7	6.4	6.2
n-Butyl-	163	$C_8H_{15}NO_4$	50.8	51.0	7.9	8.1	7.4	7.0
Allyl-[c]	184	$C_7H_{11}NO_4$	48.6	48.7	6.4	6.5	8.1	8.1
Isobutyl-	191	$C_8H_{15}NO_4$	50.8	51.2	7.9	7.7	7.4	7.6
Methyl-[d]	178	$C_5H_9NO_4$					9.5	9.5

[a] The *N*-alkyl-aspartic acids were obtained in nearly quantitative yield from their esters. [b] Insoluble in water; to prevent precipitation with barium sulfate, its solution after hydrolysis must be filtered hot. May be hydrolyzed at room temperature with (2*N*) sodium hydroxide. [c] Evaporation of the solution after hydrolysis left an oil which crystallized from hot water–methanol and the addition of acetone. [d] Same m.p. as reported in Beilstein, *Organische Chemie* (*cf.* ref. 6).

TABLE III

PREPARATION OF N^2-ALKYL-DL-α-ASPARAGINES

Substance, N^2-Alkyl-DL-α-asparagine	Yield,[a] %	M.P., °C.	Formula	Carbon, %		Hydrogen, %		Nitrogen, %	
				Calcd.	Found	Calcd.	Found	Calcd.	Found
Cyclohexyl-	71	181	$C_{10}H_{18}N_2O_3$	56.0	55.8	8.4	8.5	13.1	12.5
n-Hexyl-[b]	85	160	$C_{10}H_{20}N_2O_3$	55.5	55.1	9.3	9.1	12.9	12.4
n-Butyl-	73	193	$C_8H_{16}N_2O_3$	51.1	51.1	8.5	8.5	14.9	14.7
Allyl-	76	175	$C_7H_{12}N_2O_3$	48.8	48.4	6.9	6.9	16.2	15.7
Isobutyl-	83	170	$C_8H_{16}N_2O_2$	51.0	51.0	8.5	8.5	14.9	14.7
Methyl-[c]	80	191	$C_5H_{10}N_2O_3 + H_2O$					17.1	17.1

[a] Yields reported are from the "mixed anhydride" method. [b] Using the "anhydride hydrochloride" method gave 44% yield. [c] The substance sinters around 115°, due to loss of water of crystallization, resolidifies and melts at 191°. Same m.p as reported in *Beilstein*, Organische Chemie (*cf.* ref. 6).

dryness of the ammonia solution on a water bath, was triturated with acetone and filtered. The substances were recrystallized from a minimum quantity of hot water, a large volume of acetone was added and left overnight in an ice box to complete precipitation. (For the N^2-cyclohexyl-α-asparagine ether was also added to help crystallization.)

Method II. To dry *N*-alkyl-aspartic acid (1 g.) held in a glass-stoppered flask, 5 ml. acetic acid and 5 ml. acetyl chloride were added, shaken until solution was complete, and left overnight at room temperature. Generally, the anhydride hydrochloride precipitated, otherwise dry ether was added. It was filtered, washed with dry ether, and dried in a vacuum desiccator for a short time. The dry substance was added to 20 ml. concentrated ammonia solution, left at room temperature for 20 min. and evaporated on a water bath. Purification of the N^2-alkyl-α-asparagine was carried out as before.

The N^2-alkyl-α-asparagines thus prepared are listed in Table III.

JERUSALEM, ISRAEL

[CONTRIBUTION FROM THE FULMER CHEMICAL LABORATORY, STATE COLLEGE OF WASHINGTON]

Cortical Steroid Analogs. III. Further Synthetic and Structure Studies on Acyclic Dihydroxyacetones Derived from 2,3-Butanedione. 1,3-Dihydroxy-3-phenyl-2-butanone[1]

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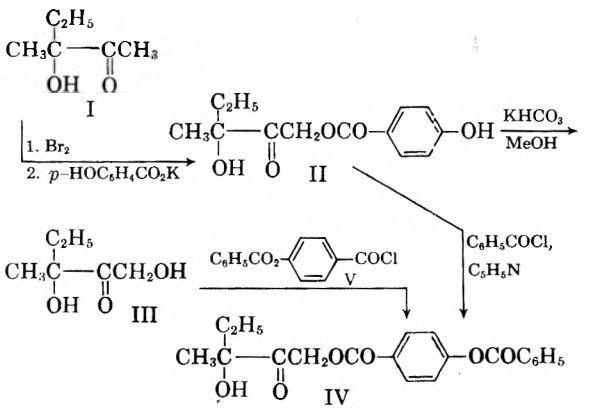
Received February 9, 1959

Methods previously employed in the synthesis of 1,3-dihydroxy-3-methyl-2-pentanone (III) failed when applied to 1,3-dihydroxy-3-phenyl-2-butanone (X). Because of this, a study of other ester intermediates which might be employed in this synthesis, was undertaken. 1-(*p*-Hydroxybenzoates) could not be converted readily to dihydroxyacetones; however, hydrolysis of the 1-(*p*-nitrobenzoate) and 1-(*p*-chlorobenzoate) of X led to the synthesis of the desired 1,3-dihydroxy-3-phenyl-2-butanone (X) in good yields (44–66%). Structural relationships between III and its 1-(*p*-hydroxybenzoate) II, as well as the dihydroxyacetone X and its 1-(*p*-nitrobenzoate) IX are described; IX can be cleaved by periodic acid to *O*-*p*-nitrobenzoylglycolic acid (XI) and acetophenone. The alkaline instability of X resulting in the formation of acetophenone has been investigated, and an explanation for this behavior is presented. Compound X showed no significant corticoid, thymolytic, or antiinflammatory activity in assays on adrenalectomized rats.

Although the synthesis of certain types of acyclic dihydroxyacetone derivatives apparently has not been described previously, Diels and Johlin had discussed an attempted synthesis of two such compounds,[3] 1,3-dihydroxy-3-methyl-2-pentanone (III) and 1,3-dihydroxy-3-phenyl-2-butanone (X). Dihydroxyacetones have been of interest in this laboratory as cortisone analogs, and as a part of our program, we recently succeeded in synthesizing compound III starting with 2,3-butanedione.[1] We now report the synthesis of the other dihydroxyacetone, which had been of interest to Diels and Johlin,[3] compound X; experiments confirming the structure of both X and III are also presented.

When the scheme that had been employed for the synthesis of III was applied in the case of X,[1] difficulties were encountered at two stages. If an attempt was made to convert 3-hydroxy-3-phenyl-2-butanone to the corresponding 1-acetate, a reaction mixture resulted, from which a pure product could not be obtained. However, the crude 1-acetate appeared to be at hand, because a corresponding semicarbazone could be isolated from the reaction mixture. Still, it was not possible to produce the desired dihydroxyacetone from the crude 1-acetate, for when this substance was treated in the usual manner with potassium bicarbonate-methanol,[1] an intractable sirup was formed. In an attempt to form a solid derivative from this reaction mixture, it was found that treatment with 2,4-dinitrophenylhydrazine produced a small amount of acetophenone 2,4-dinitrophenylhydrazone. An experiment, to be described subsequently, indicates how this product probably was formed.

Because of these difficulties, it appeared strategic to synthesize crystalline ester intermediates by derivation from aromatic acids. Also, it seemed wise to conduct initial experiments of this nature in the series relating to the dihydroxyacetone III which had been previously prepared.[1] Accordingly, the intermediate bromo ketone, prepared from 3-hydroxy-3-methyl-2-pentanone (I), was heated under reflux in acetone with potassium *p*-hydroxybenzoate, and, indeed, a nicely crystalline 1-(*p*-hydroxybenzoate) intermediate II was formed. The structure of II and the previously prepared dihydroxyacetone III were compared by the following interrelationships. The 1-(*p*-hydroxybenzoate) II readily underwent benzoylation to give the derivative IV, identical with the substance formed by the reaction of the acid chloride V with a sample of III. The acid chloride V had not been previously reported but was readily prepared from the corresponding known acid.[4] Methanolysis of the



(1) Presented in part before the Division of Organic Chemistry at the 130th Meeting of the American Chemical Society, Atlantic City, N. J., Sept. 20, 1956, and in part before the Northwest Scientific Association, Spokane, Wash., Dec. 27, 1957. Paper II, G. W. Stacy, R. A. Mikulec, S. L. Razniak, and L. D. Starr, *J. Am. Chem. Soc.*, 79, 3587 (1957).

(2) In part abstracted from theses submitted by Richard A. Mikulec and Laurence D. Starr, respectively, in partial fulfillment of the requirements for the degree of Doctor of Philosophy, State College of Washington, June, 1956, 1955.

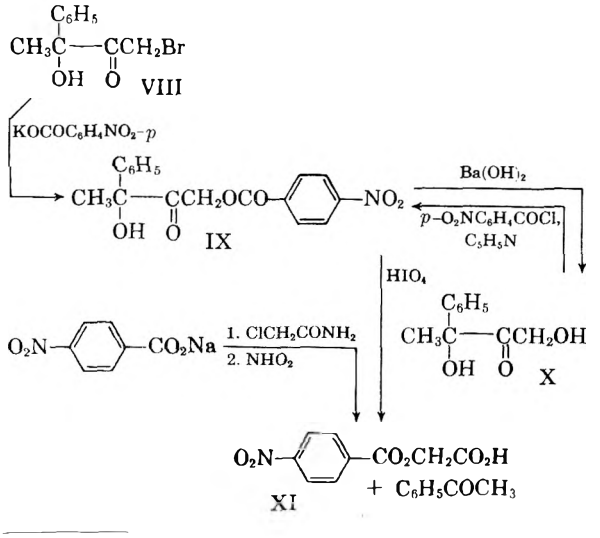
(3) O. Diels and J. M. Johlin, *Ber.*, 44, 403 (1911).

(4) K. V. Rao and T. R. Seshadri, *J. Chem. Soc.*, 122 (1947).

1-(*p*-hydroxybenzoate) II gave a low yield of III along with a substantial recovery of unreacted II.

When these procedures were extended to the phenyl series, discrepancies were revealed. Attempted formation of a 1-(*p*-hydroxybenzoate) gave what appeared to be 1,3-dihydroxy-3-phenyl-2-butanone 1-(*p*-hydroxybenzoate) (VI); however, repeated endeavor to obtain this substance in a state of analytical purity met with failure. Various samples, obtained by chromatography or recrystallization, gave results about 1% high on the carbon analysis. This analytically impure product could be accounted for by occlusion of benzene, and it did give a pure benzoyl derivative VII in a 74% yield. Attempts to convert the impure 1-(*p*-hydroxybenzoate) VI by methanolysis to the desired dihydroxyacetone failed, giving recovered starting material and a small amount of acetophenone.

A continuation of our search for appropriate ester intermediates led to the 1-(*p*-nitrobenzoate) (IX), the basis of selection being the relative ease of hydrolysis of ethyl *p*-nitrobenzoate.[5] It was found that 1,3-dihydroxy-3-phenyl-2-butanone 1-(*p*-nitrobenzoate) (IX) was obtained in significantly better yields than had been the case with the corresponding 1-(*p*-hydroxybenzoate). In an attempt to obtain X, methanolysis of IX gave a reddish-brown oil; however, it appeared certain that removal of the *p*-nitrobenzoate group had taken place, as methyl *p*-nitrobenzoate was isolated. This suggested that the failure to obtain the dihydroxyacetone X might well be due to its sensitivity to the prolonged alkaline conditions of the reaction. It seemed possible that a procedure involving a shorter exposure, as well as mild alkaline conditions, might be more suitable. Such a procedure had been employed by Smith and Anderson for the hydrolysis of phenyldihydroxyacetone diacetate by barium hydroxide solution at 0°.[6] Extension of precisely the same procedure failed, as had the methanolysis; however, a modification, employing considerably less barium hydroxide, resulted finally in the synthesis of 1,3-dihydroxy-3-phenyl-2-butanone (X) in yields as high as 66%.



The dihydroxyacetone X, like its predecessor III, was characterized by its ability to reduce Benedict's solution and Tollen's reagent, an infrared absorption spectrum consistent with the structure assigned, and the formation of a 2,4-dinitrophenylhydrazone. It was also possible to reconvert X to the 1-(*p*-nitrobenzoate) IX by reaction with *p*-nitrobenzoyl chloride in pyridine. Further evidence for the structure of IX, and hence X, was obtained by the periodic acid oxidation of IX to yield *O*-*p*-nitrobenzoylglycolic acid (XI) and acetophenone. For comparison, it was necessary to prepare an authentic sample of XI (previously unreported) from the corresponding amide, which had been synthesized by Einhorn and Seuffert by the reaction of sodium *p*-nitrobenzoate and chloroacetamide.[7] The amide was converted to the desired acid by treatment with nitrous acid under conditions critical to success of the reaction.

Of further interest was the preparation of a 1-(*p*-chlorobenzoate) intermediate XII in a yield approximating that which had been obtained for IX. The 1-(*p*-chlorobenzoate) XII also was hydrolyzed by the barium hydroxide procedure to give X in good yield.

Now that the dihydroxyacetone X was at hand, it was of interest to explain the formation of acetophenone in the experiments on the methanolysis of the crude 1-acetate and 1-(*p*-hydroxybenzoate), which were discussed earlier. Therefore, the pure dihydroxyacetone X was submitted to similar conditions by stirring in methanolic potassium bicarbonate for 2 days, and X, indeed, proved to be unstable forming a small amount of acetophenone. In parallel with our observations, the the alkaline instability of the dihydroxyacetone side chain in steroids has been noted in at least two instances.[8,9] Wendler and Graber[9] have observed that 3α, 17α, 21-trihydroxypregnane-11,20-dione is converted by dilute methanolic potassium hydroxide under nitrogen to 3α-hydroxyetiocholane-11,17-dione. These authors suggest that the course of the reaction involves a retroaldolization of the equilibrium aldotriose. A similar explanation may be advanced in the present instance for the formation of acetophenone from X.

Biological evaluation. 1,3-Dihydroxy-3-phenyl-2-butanone (X) and its 1-(*p*-nitrobenzoate) IX

(5) L. P. Hammett, *Physical Organic Chemistry*, McGraw-Hill Book Co., New York, N. Y., 1940, p. 121.

(6) L. I. Smith and R. H. Anderson, *J. Org. Chem.*, **16**, 963 (1951).

(7) A. Einhorn and R. Seuffert, *Ber.*, **43**, 2995 (1910).

(8) H. L. Mason, *Proc. Mayo Clin.*, **13**, 235 (1938).

(9) N. L. Wendler and R. P. Graber, *Chem. and Ind. (London)*, 549 (1956).

were investigated for possible corticoid activity by the glycogen deposition assay in adrenalectomized rats. No significant activity was observed in either case, and even when a massive dose of lg./kg. of X was administered, no response was noted. Further, no response was observed in either case for thymolytic and anti-inflammatory assays in adrenalectomized rats.

EXPERIMENTAL[10]

1,3-Dihydroxy-3-phenyl-2-butanone 1-acetate semicarbazone. The intermediate bromo ketone VIII was obtained by the addition of 14.1 g. (0.086 mole) of bromine in 200 ml. of chloroform over a period of 2 hr. to 14.0 g. (0.085 mole) of 3-hydroxy-3-phenyl-2-butanone[11] in 400 ml. of chloroform. Throughout, the reaction mixture was stirred, and after addition of bromine had been completed, stirring was continued for 1 hr., at the end of which time only a small amount of free bromine remained. The reaction mixture was washed with dilute sodium bisulfite solution (9 × 100 ml.) and once with water (100 ml.). The chloroform solution was dried over 100 g. of anhydrous sodium sulfate, containing 0.1 g. of magnesium oxide.[12] After the solvent had been removed, the residual, crude bromo ketone was employed immediately in the next step.

A mixture of 42.7 g. of potassium bicarbonate, 230 ml. of acetone, and 26.9 g. of glacial acetic acid was heated under reflux for 1 hr. with stirring and then was cooled in an ice bath. The crude bromo ketone VIII from above, in 50 ml. of acetone, was added dropwise with stirring to the acetone–potassium acetate mixture over a period of 1 hr. The resulting mixture was heated under reflux for 16 hr. Dissolved potassium acetate was precipitated by stirring and cooling the reaction mixture in an ice bath for 1 hr. Removal of the acetone by distillation through a 30-cm. Vigreux column gave 7.15 g. (38% yield) of a brown residue. Attempts to crystallize or distill this material either by conventional methods or by a molecular distillation failed.

A semicarbazone was prepared from 1.00 g. (4.5 mmoles) of the above crude product and 1.00 g. (9.0 mmoles) of semicarbazide hydrochloride in ethanol-water. The crude product (820 mg.) was recrystallized from ethanol-water to give 620 mg. (49% yield) of colorless needles, m.p. 185.5–186°. A second recrystallization raised the melting point to 187.4–187.5°.

Anal. Calcd. for $C_{13}H_{17}N_3O_4$: C, 55.90; H, 6.14; N, 15.04. Found: C, 55.91; H, 6.31; N, 15.13.

Attempted conversion of the crude 1-acetate to 1,3-dihydroxy-3-phenyl-2-butanone (X). A mixture of crude 1-acetate (obtained from 14.0 g. of 3-hydroxy-2-butanone, as described above), 64.0 g. of potassium bicarbonate, and 320 ml. of methanol was stirred under nitrogen for 2 days. After the reaction mixture had been cooled in an ice bath, it was filtered and concentrated. The resulting cake was triturated with cold acetone, and the mixture was filtered. Removal of the acetone under reduced pressure produced 19.1 g. of a dark brown, tar-like product.

Attempted isolation of product as a derivative, when 2.00 g. of the crude reaction mixture was treated with 2,4-dinitrophenylhydrazine, gave, after two recrystallizations from 1,4-dioxane-ethanol, 220 mg. of red-orange needles; m.p. 246°. This substance gave an analysis consistent with the composition of acetophenone 2,4-dinitrophenylhydrazone, lit.[13] m.p. 240–241°; a mixed melting point determination with an authentic sample showed no depression.

1,3-Dihydroxy-3-methyl-2-pentanone 1-(p-hydroxybenzoate) (II). To form potassium *p*-hydroxybenzoate, a mixture of 20.0 g. (0.20 mole) of potassium bicarbonate and 29.1 g. (0.21 mole) of *p*-hydroxybenzoic acid in 240 ml. of acetone was heated under reflux for 0.5 hr. The crude bromo ketone intermediate, obtained from 4.65 g. (0.040 mole) of I and 6.47 g. (0.0405 mole) of bromine,[1] was dissolved in 30 ml. of acetone and was added dropwise with stirring to the refluxing acetone-potassium *p*-hydroxybenzoate suspension. The resulting mixture was heated under reflux for 20 hr., cooled, and filtered. The filtrate was evaporated under reduced pressure, and the residue was suspended in 150 ml. of 5% sodium bicarbonate solution. The suspension was extracted with chloroform (4 × 100 ml.), and the extracts were combined, dried over anhydrous sodium sulfate, and evaporated under reduced pressure to give 5.86 g. (58% yield) of crude product, m.p. 103–114°. One recrystallization from chloroform gave 3.22 g. (32% yield) of colorless plates, m.p. 114.5–115.5°. An analytical sample was prepared by three additional recrystallizations from chloroform, m.p. 116–117°.

Anal. Calcd. for $C_{13}H_{16}O_5$: C, 61.89; H, 6.39. Found: C, 61.67; H, 6.37.

1,3-Dihydroxy-3-methyl-2-pentanone 1-(p-benzoyloxybenzoate) (IV) *from* II. A solution of 0.50 g. (2.0 mmoles) of II and 0.28 g. (2.0 mmoles) of benzoyl chloride in 3.0 ml. of pyridine was heated on a steam bath for 1 min. and then poured into 10 ml. of water with vigorous stirring. The resulting precipitate was washed with 5% sodium carbonate solution and water to give 0.63 g. (89% yield) of colorless needles, m.p. 101.5–102.5°. Recrystallization from aqueous acetone or carbon tetrachloride gave sharp-melting products (m.p. 102.5–103°) which, however, did not give analytical data in close agreement with the calculated values. Finally, an analytical sample was obtained by suspending the compound on the alumina column and eluting with benzene-ether (1:1), m.p. 103–103.5°.

Anal. Calcd. for $C_{20}H_{20}O_6$: C, 67.40; H, 5.66. Found: C, 67.82; H, 5.43.

p-Benzoyloxybenzoyl chloride (V). To a suspension of 4.84 g. (0.020 mole) of *p*-benzoyloxybenzoic acid[4] in 17 ml. of carbon tetrachloride was added 4.60 g. (0.022 mole) of phosphorus pentachloride with warming on a steam bath until a clear solution resulted. This solution was evaporated to dryness under reduced pressure, and the residue was recrystallized twice from carbon tetrachloride to give 4.46 g. (86% yield) of large, hard clumps of colorless burrs, m.p. 131–132°.

Anal. Calcd. for $C_{14}H_9ClO_3$: C, 64.50; H, 3.48; Cl, 13.60. Found: C, 64.36; H, 3.51; Cl, 13.45.

1,3-Dihydroxy-3-methyl-2-pentanone 1-(p-benzoyloxybenzoate) (IV) (*from the dihydroxyacetone* III). A mixture of 264 mg. (2.0 mmoles) of III[1] and 521 mg. (2.0 mmoles) of V in 3.0 ml. of pyridine was warmed on a steam bath for 15 min. and poured into 20 ml. of water. The resulting precipitate was removed by filtration and washed with 5% sodium carbonate solution (3 × 2 ml.) and water, and 501 mg. (70% yield) of a colorless solid, m.p. 96–99°, was obtained. This material was suspended on a column of 40 g. of alumina, which was eluted with 150 ml. of benzene-ether (1:1) to yield 368 mg. (52%) of colorless needles, m.p. 102.5–103.5°. This substance was shown by a mixed melting point determination (m.p. 102–103.5°) and by similarity of

(10) All melting points are corrected, and boiling points are uncorrected. The microanalytical work was performed by Weiler and Straus Laboratories, Oxford, England, and Galbraith Laboratories, Knoxville, Tenn. The infrared absorption spectra were determined by a Perkin-Elmer Double Beam Infrared Spectrometer, Model 21; the solid samples were dispersed in potassium bromide disks.

(11) Prepared in a 48% yield by the method of J. Wegmann and H. Dahn, *Helv. Chim. Acta*, **29**, 101 (1946).

(12) Magnesium oxide is said to stabilize α-bromo ketones; J. R. Catch, D. F. Elliott, D. H. Hey, and E. R. H. Jones, *J. Chem. Soc.*, 272 (1948).

(13) H. E. Zimmerman and J. English, *J. Am. Chem. Soc.*, **76**, 2294 (1954).

infrared spectra to be identical with the 1-(*p*-benzoyloxybenzoate) formed from II, which was described above.

1,3-Dihydroxy-3-phenyl-2-butanone 1-(p-hydroxybenzoate) (VI). The crude bromo ketone VIII, obtained from the reaction of 6.57 g. (0.040 mole) of 3-hydroxy-3-phenyl-2-butanone and 6.47 g. (0.0405 mole) of bromine, in 30 ml. of acetone was added to an acetone–potassium *p*-hydroxybenzoate mixture in a manner similar to that used for the preparation of II above. After the mixture had been worked up similarly, there was obtained 4.11 g. (34% yield) of a solid, m.p. 93–97°. Six recrystallizations from benzene gave a product of constant melting point but consistently lower than the original crude material, m.p. A 88.5–92.5°. A sample of the substance was also chromatographed on an alumina column by eluting with benzene-ether (1:1), m.p. B 90–92°.

Anal. Calcd. for $C_{17}H_{16}O_5$: C, 67.99; H, 5.87; $C_{17}H_{16}O_5 \cdot {}^1/_6C_6H_6$: C, 68.90; H, 5.47. Found: C, A 68.85, B 68.90; H, A 5.44, B 5.58.

1,3-Dihydroxy-3-phenyl-2-butanone 1-(p-benzoyloxybenzoate) (VII). By a procedure similar to that employed in the preparation of IV from II, as described above, 0.60 g. (2.0 mmoles) of VI and 0.28 g. (2.0 mmoles) of benzoyl chloride in 3.0 ml. of pyridine yielded 0.73 g. (90%) of colorless needles, m.p. 112–113°. Recrystallization from carbon tetrachloride raised the melting point to 112.5–113.5° (0.60 g.; yield, 74%).

Anal. Calcd. for $C_{24}H_{20}O_6$: C, 71.28; H, 4.98. Found: C, 71.09; H, 5.03.

Methanolysis experiments on 1-(p-hydroxybenzoates). A. Compound II. A mixture of 5.05 g. (0.020 mole) of II and 14.5 g. of potassium bicarbonate in 75 ml. of methanol was stirred at room temperature under nitrogen for 2 days and then was allowed to stand for an additional day. The mixture was filtered, and the solid was washed throughly with methanol. The filtrate was concentrated under reduced pressure and distilled through a 15-cm. Vigreux column. There was obtained 270 mg. (10% yield) of the dihydroxyacetone VI; b.p. 51° (0.15 mm.), n_D^{25} 1.4545, lit.[1] b.p. 51–58.5° (0.1–0.25 mm.), n_D^{25} 1.4548.

The residue from the distillation was crystallized from chloroform to yield 2.82 g. (54% recovery) of unreacted II, m.p. 112.5–116°, mixed m.p. 114–116.5°. From the solid which had been filtered off from the reaction mixture, there was obtained, upon dissolving it in water and acidifying the solution, 413 mg. (15% yield) of *p*-hydroxybenzoic acid, m.p. 213.5–214.5°, lit.[14] m.p. 214–215°, mixed m.p. 213.5–214.5°.

B. Compound VI. A mixture of 1.17 g. (3.9 mmoles) of VI and 2.84 g. of potassium bicarbonate in 15 ml. of methanol was treated as above. The mixture was filtered, the solid was washed with methanol and the filtrate was concentrated under reduced pressure. The residue was taken up in 25 ml. of benzene and washed with water (2 × 5 ml.). The benzene solution was dried over anhydrous sodium sulfate and evaporated to yield 0.34 g. of yellow crystals; recrystallization of this crude substance from ether-ligroin (b.p. 35–60°) gave 0.23 g. (19% recovery) of VI, m.p. 81–93°, mixed m.p. 88–95°. None of the desired dihydroxyacetone X was isolated.

Since the aqueous washings from above possessed an odor of acetophenone, they were added to 100 ml. of 2*N* hydrochloric acid saturated with 2,4-dinitrophenylhydrazine. From this mixture there was obtained a gummy solid, which was recrystallized from ethyl acetate–ethanol to yield 8 mg. of impure acetophenone 2,4-dinitrophenylhydrazone; m.p. 230–235°, mixed m.p. 238–240°.

1,3-Dihydroxy-3-phenyl-2-butanone 1-(p-nitrobenzoate) (IX). As a result of a number of experiments, the most convenient procedure for preparing the intermediate bromo ketone VIII was found to involve the addition of 1 ml. of a solution of 16.8 g. (0.105 mole) of bromine in 225 ml. of chloroform (reagent) with stirring to 16.4 g. (0.10 mole) of 3-hydroxy-3-phenyl-2-butanone[11] in 475 ml. of chloroform to which a few drops of acetic acid had been added; the mixture was warmed until the color of bromine disappeared. The bromine solution was then added as rapidly as possible (maintenance of a straw-colored solution); a period of 20 min. was required. The solution was stirred for an additional 15 min. while being cooled in an ice bath. After the solution had been washed with cold 5% sodium hydroxide solution (115 ml.) and saturated sodium chloride solution (2 × 65 ml.), it was dried over anhydrous sodium sulfate to which 0.3 g. of magnesium oxide had been added.[12] The chloroform was removed by distillation *in vacuo*, and the residual bromo ketone was taken up immediately in 40 ml. of acetone in preparation for the next step.

A mixture of 50.1 g. (0.50 mole) of potassium bicarbonate and 87.7 g. (0.52 mole) of *p*-nitrobenzoic acid in 1750 ml. of acetone was heated under reflux for 0.5 hr. to form potassium *p*-nitrobenzoate. To this was added dropwise with stirring the acetone solution of bromo ketone (above). The resulting mixture was heated under reflux for 20 hr. with stirring and then allowed to stand for an additional 20 hr. at room temperature without stirring. The mixture was filtered, and the solid was washed with acetone. The filtrate was concentrated under reduced pressure until bumping commenced. To the residue was added 375 ml. of 5% sodium bicarbonate solution with shaking, which caused crystallization of the residual oil. The large lumps were broken up, filtered, and washed with water to give 22.4 g. (68% yield) of a light brown solid, m.p. 105.5–107.5°. Recrystallization from carbon tetrachloride gave 19.0 g. (58% yield) of small, light tan needles, m.p. 108–108.5°.

Anal. Calcd. for $C_{17}H_{15}NO_6$: C, 62.00; H, 4.59; N, 4.25. Found: C, 61.85; H, 4.52; N, 3.97.

The infrared absorption spectrum showed bands that were assignable to OH stretching frequency (3425 cm.$^{-1}$, m), *t*-OH (1350 cm.$^{-1}$, s; 1130 cm.$^{-1}$, m), C=O (1725 cm.$^{-1}$, s), and NO_2 (1530 cm.$^{-1}$, s; 1350 cm.$^{-1}$, s).

1,3-Dihydroxy-3-phenyl-2-butanone 1-(p-chlorobenzoate) (XII). The procedure was identical with that above for IX. From identical quantities of reagents and solvents and 82.2 g. (0.525 mole) of *p*-chlorobenzoic acid was obtained 23.0 g. (72% yield) of a tan product, m.p. 99–105°. Two recrystallizations from carbon tetrachloride gave 16.6 g. (52%) of light tan crystals, m.p. 107–108°. An analytical sample was prepared by further recrystallization from carbon tetrachloride, m.p. 108–108.5°.

Anal. Calcd. for $C_{17}H_{15}ClO_4$: C, 64.05; H, 4.74; Cl, 11.12. Found: C, 63.84; H, 4.46; Cl, 11.05.

Attempted methanolysis of IX *to* X. The 1-(*p*-nitrobenzoate) IX (6.60 g., 0.020 mole) was treated as in the methanolysis experiment A above. A part (417 mg.) of the methanol-washed solid was water insoluble and was identified as methyl *p*-nitrobenzoate; m.p. 96–97°, lit.[15] m.p. 96–96.5°, mixed m.p. 95.5–96.5°. The methanol solution was evaporated under reduced pressure to yield a residue, which was extracted with ether and then with acetone. When it was dissolved in water and the solution acidified, the solid insoluble in the solvents yielded 58 mg. of *p*-nitrobenzoic acid; m.p. 217–225°, lit.[16] m.p. 238°. Recrystallization from water raised the melting point to 238–239°, mixed m.p. 239–240°. The ether and acetone extracts from above were evaporated *in vacuo*, and the residue was crystallized from aqueous methanol to give 2.60 g. of methyl *p*-nitrobenzoate (total yield 71%), m.p. 90–93.5°; recrystallization from ligroin (b.p. 66–75°) raised the melting point to 94.5–95.5°. The mother liquors were concentrated to yield 2.60 g. of a reddish-brown oil which could not be induced to crystallize from any of the common solvents, nor distilled without decomposition.

(14) R. Willstätter and W. Mieg, *Ann.*, 408, 61 (1915).

(15) W. E. Caldwell and K. R. Mac Lean, *J. Am. Chem. Soc.*, 55, 3458 (1933).

(16) E. Widmann, *Ann.*, 193, 202 (1878).

1,3-Dihydroxy-3-phenyl-2-butanone (X). A. *From the 1-(p-nitrobenzoate)* IX. A solution of 3.29 g. (0.010 mole) of IX in 200 ml. of 95% ethanol was cooled to 0°. To this was added an ice-cold solution of 1.75 g. (1.1 equiv.) of barium hydroxide octahydrate in 85 ml. of boiled water. The addition was carried out over a period of 1 hr., and then the weakly basic (*p*H 8) mixture was stirred at 0° for 2 hr. The resulting solution was concentrated under reduced pressure to a small volume and was extracted with ether (1 × 75 ml., 5 × 15 ml.). The ether extracts were combined, washed with 20 ml. of 5% sodium bicarbonate solution, and dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure gave 1.56 g. (87% yield) of crude X, m.p. 60.5–66°. Recrystallization from carbon tetrachloride afforded 1.20 g. (66% yield, yields in several other runs ranged from 44–63%) of colorless needles, m.p. 69.5–70°. Two additional recrystallizations from carbon tetrachloride furnished an analytical sample, m.p. 70–70.5°.

Anal. Calcd. for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.68; H, 6.89.

The above material reduced Benedict's solution and Tollen's reagent and gave an infrared absorption spectrum, which showed bands that were assignable to OH stretching frequency (3410 cm.$^{-1}$, s), *t*-OH (1365 cm.$^{-1}$, w), and C=O (1715 cm.$^{-1}$, s).

A *2,4-dinitrophenylhydrazone* was prepared in a manner similar to that employed for that of III.[1] Small clumps of yellow needles were obtained from benzene-methanol in a 28% yield, m.p. 173.5–174°.

Anal. Calcd. for $C_{16}H_{16}N_4O_6$: C, 53.33; H, 4.48; N, 15.55. Found: C, 53.26; H, 4.70; N, 15.74.

B. From the 1-(p-chlorobenzoate) XII. Hydrolysis of 3.19 g. (0.01 mole) of XII was carried out by essentially the same procedure and involving the same quantities of reagents as in the case of IX above. Crude X was obtained in a yield of 1.28 g. (71%), m.p. 61–66°. Recrystallization from carbon tetrachloride gave 928 mg. (52%) of relatively pure X, m.p. 68–69°.

Formation of the 1-(p-nitrobenzoate) IX *from* X. A mixture of 180 mg. (1.0 mmole) of the dihydroxyacetone X and 186 mg. (1.0 mmole) of recrystallized *p*-nitrobenzoyl chloride in 1.5 ml. of pyridine was warmed on a steam bath for 15 min. and poured into 10 ml. of water. It was necessary to cool the mixture overnight before the resulting oil solidified. The solid was filtered off and washed with 5% sodium carbonate solution (3 × 1 ml.) and with water. There was obtained 172 mg. (52% yield) of IX, m.p. 106.5–107.5°. Recrystallization from chloroform gave 151 mg. (46% yield), m.p. 107.5–108°. A mixture of this substance with IX formed from the bromo ketone VIII resulted in no depression in melting point (108–108.5°), and the infrared spectra of these two substances were identical.

Authentic O-p-nitrobenzoylglycolic acid (XI). A solution of 897 mg. (4.0 mmoles) of *O-p*-nitrobenzoylglycolamide[7] in 10 ml. of concentrated sulfuric acid was cooled in an ice bath. An ice cold solution of 1.64 g. of sodium nitrite in 3 ml. of water was added dropwise with stirring over a period of 0.5 hr. The mixture was allowed to warm to room temperature and diluted with 50 ml. of water. The resulting precipitate was removed by filtration, washed with water, and dried to give 748 mg. (83% yield) of a light yellow solid, m.p. 144–145.5°. Recrystallization from benzene afforded 631 mg. (70% yield) of light yellow plates, m.p. 146–147°.

Anal. Calcd. for $C_9H_7NO_6$: C, 48.01; H, 3.13; N, 6.22. Found: C, 47.87; H, 3.07; N, 6.25.

Periodic acid oxidation of the 1-(p-nitrobenzoate) IX. A solution of 165 mg. (0.5 mmole) of IX in 10 ml. of methanol was treated with 1.85 ml. of 0.54 *M* periodic acid solution, and the mixture was allowed to stand at room temperature for 1 hr. with occasional swirling. The reaction mixture was distilled to dryness under reduced pressure, the distillate being collected in a Dry Ice-cooled receiver. To the distillate was added 50 ml. of 2*N* hydrochloric acid saturated (at 5°) with 2,4-dinitrophenylhydrazine.[17] After dilution with 10 ml. of 2*N* hydrochloric acid, the mixture was allowed to remain at 5° for 2 hr. The precipitate was collected in a coarse fritted-glass filter and washed with 25 ml. of 2*N* hydrochloric acid and with distilled water until the washings gave a negative test for chloride ion with silver nitrate solution. After the precipitate had been dried to constant weight, there was obtained 137 mg. (91% yield) of acetophenone 2,4-dinitrophenylhydrazone, m.p. 239–240.5°, mixed m.p. 241–242°. The residue from the distillation was suspended in a small volume of water, filtered, washed with water, and dried to give 101 mg. (89% yield) of *O-p*-nitrobenzoylglycolic acid (XI), m.p. 146–147°, mixed m.p. 146–147°.

Alkaline decomposition of the dihydroxyacetone X. A mixture of 329 mg. (1.0 mmole) of X and 0.72 g. of potassium bicarbonate in 5 ml. of methanol was stirred under nitrogen for 2 days; the reaction mixture was then allowed to stand for an additional day. The mixture was filtered, and the filter cake was washed well with methanol. The filtrate and washings were evaporated (without heating) under reduced pressure, the distillate being collected in a receiver immersed in a Dry Ice bath. To the distillate was added 100 ml. of 2*N* hydrochloric acid saturated (at 5°) with 2,4-dinitrophenylhydrazine; the mixture was maintained at 5° for 2 hr. By a procedure similar to that described above, 34 mg. (11% yield) of acetophenone 2,4-dinitrophenylhydrazone was isolated, m.p. 237–239°, mixed m.p. 241–242°.

Acknowledgment. This investigation was supported in part by a research grant (A-253, C2-C4) and in part by a predoctoral fellowship to R.A.M. (AF-5336) from the National Institute of Arthritis and Metabolic Diseases, Public Health Service. For biological evaluations, we wish to extend our thanks to Mr. S. C. Lyster and Mr. L. E. Barnes, Department of Endocrinology, The Upjohn Co., Kalamazoo, Mich., and to a group under the direction of Dr. Erwin P. Vollmer, Consultant in Endocrinology, National Service Center, Public Health Service, Bethesda, Md. For determination of infrared absorption spectra, we wish to thank Mr. George D. Wagner and Mr. David L. Frasco of the Division of Industrial Research and Mr. Roland W. Lovejoy of the Department of Chemistry, State College of Washington.

PULLMAN, WASH.

(17) Determination of ketones as 2,4-dinitrophenylhydrazones is based on the procedure of H. A. Iddles, A. W. Low, B. D. Rosen, and R. T. Hart, *Ind. Eng. Chem., Anal. Ed.*, 11, 102 (1939).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF LOUISVILLE]

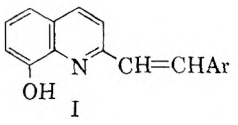
Styryl Derivatives of 8-Quinolinol

J. P. PHILLIPS, RICHARD BREESE, AND EDWARD M. BARRALL

Received February 11, 1959

Ultraviolet and infrared spectra of 15 styryl derivatives of 8-quinolinol indicate that these compounds belong to the *trans* series.

Condensations of aromatic aldehydes with 8-hydroxyquinaldine or 8-hydroxylepidine in acetic anhydride yield respectively 2 or 4 substituted styryl-8-hydroxyquinolines (I and II). Fifteen new compounds of this type with hydroxyl and methoxyl substituents have been prepared (Table I) to examine for chelating properties toward metals and to use as intermediates for the preparation of formaldehyde resins containing chelating centers.



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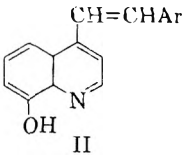


II

in cold ethanol or water containing hydrochloric acid. The solubility of 2-*p*-hydroxystyryl-8-hydroxyquinoline hydrochloride in 5% aqueous hydrochloric acid, for example, is less than 0.1 g. per liter.

The question of whether these compounds are *cis* or *trans* isomers is of interest in determining whether hydroxyl groups located in the styryl part of the molecule could participate in chelation. This could happen only in the *cis* isomers, but these would have somewhat crowded structures and are therefore not as likely to be stable as the *trans* compounds. Infrared spectra of all the hydrochlorides as well as several of the free bases prepared from them show the 10.38 μ band associated with *trans* RCH:CHR′ structures, especially stilbenes,[2] but not the 10.88 and 12.8 μ. bands expected for the corresponding *cis* isomers. Ultraviolet spectra in acidic ethanol were also determined (Table II). Except for the 4-styryl derivatives and the naphthyl substituted compounds which would be reasonably expected to show the differences observed, these spectra are very similar both to each other and to like compounds previously prepared

TABLE I

2-STYRYL-8-HYDROXYQUINOLINE HYDROCHLORIDES

No	Ar in Formula I	Formula	M.P., °C.	Yield, %	Nitrogen	
					Calcd.	Found
1	2,5-(OH)(Cl)C_6H_3	$C_{17}H_{12}ClNO_2$·HCl	198	67	4.19	4.32
2	2,5-(OH)(Br)C_6H_3	$C_{17}H_{12}BrNO_2$[a]	200	62	4.09	4.15
3	2-MeOC_6H_4	$C_{18}H_{15}NO_2$·BCl	177–180	—	4.47	4.26
4	[b]	$C_{17}H_{13}NO_2$·HCl	230	25	4.66	4.59
5	4-HOC_6H_4	$C_{17}H_{13}NO_2$·HCl	235	70	4.66	4.31
6	[c]	$C_{18}H_{15}NO_2$·HCl	199	92	4.47	4.43
7	3,4-(MeO)(OH)C_6H_3	$C_{19}H_{15}NO_3$[a]	153	60	4.78	4.97
8	[d]	$C_{18}H_{15}NO_3$·HCl	212	—	4.25	3.80
9	3,4-(EtO)(OH)C_6H_3	$C_{19}H_{17}NO_3$·HCl	212–215	63	4.08	3.90
10	3,4,5-$(MeO)_3C_6H_2$	$C_{20}H_{19}NO_4$·HCl	189	35	[e]	
11	3,5,4-$(MeO)_2$(OH)C_6H_2	$C_{19}H_{17}NO_4$[a]	200–203	55	4.33	4.42
12	2,4-$(MeO)_2C_6H_3$	$C_{19}H_{17}NO_3$·HCl	172–175	60	4.07	3.82
13	2,5-$(MeO)_2C_6H_3$	$C_{19}H_{17}NO_3$·HCl	172	35	4.07	4.13
14	1-Naphthyl	$C_{21}H_{15}NO$·HCl	194	60	4.19	3.98
15	2-HO-1-naphthyl	$C_{21}H_{15}NO_2$[a]	189	90	4.47	4.19

[a] Free base. [b] 4-*o*-Hydroxystyryl-8-hydroxyquinoline hydrochloride. [c] 2-*p*-Hydroxystyryl-8-methoxyquinoline hydrochloride. [d] 4-(3′-Methoxy-4′-hydroxystyryl)-8-hydroxyquinoline hydrochloride. [e] Analyzed for carbon-hydrogen: C, calcd. 64.20; found, 63.90; H, calcd., 5.40; found, 5.83.

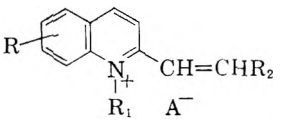
The purification of 2-styryl-8-hydroxquinoline when prepared by this method[1] has been reported to be difficult, perhaps because the reaction is incomplete and some of the aldehyde undergoes the Perkin reaction with acetic anhydride or is air-oxidized to yield acid contaminants. Similar problems in this work were found to be considerably diminished through conversion of the products to the hydrochlorides, intensely fluorescent yellow, orange or red salts with remarkably low solubility

(1) H. Irving and A. R. Pinnington, *J. Chem. Soc.*, 3782 (1954).

(2) D. F. DeTar and L. A. Carpino, *J. Am. Chem. Soc.*, **78**, 475 (1956).

TABLE II

ULTRAVIOLET AND VISIBLE SPECTRA IN EtOH-HCl OF



R	R_1	A	R_2	Wave-length Maxima, mμ (log ε)			
H	H	Cl	3,4-$OCH_2OC_6H_3$	250 (4.10)	272 (4.02)	301 (4.00)	417 (4.47)
H	Me	$MeSO_4$	3,4-$OCH_2OC_6H_3$[a]	246 (4.25)	276 (4.05)	301 (4.04)	425 (4.60)
6-OEt	H	Cl	3,4-$OCH_2OC_6H_3$		272 (3.98)	308 (4.09)	421 (4.46)
6-OEt	Me	$MeSO_4$	3,4-$OCH_2OC_6H_3$[b]		263 (4.21)	302 (4.10)	425 (4.42)
H	H	Cl	3,4-(MeO)(OH)C_6H_3[c]		261 (4.03)	310 (3.94)	430 (4.53)
H	Me	$MeSO_4$	3,4-(MeO)(OH)C_6H_3[d]	251 (4.18)	275[s] (4.03)	310 (4.04)	442 (4.51)
1[e]					267 (4.01)	309 (4.47)	407 (4.43)
2				245[s] (3.96)	—	309 (4.49)	408 (4.44)
3				245[s] (3.89)	268 (3.91)	312 (4.37)	399 (4.46)
4					262 (4.18)		424 (3.93)
5					270 (4.03)	331 (4.00)	415 (4.47)
6					270 (4.21)	328 (4.12)	420 (4.57)
7					280 (4.17)	323 (4.14)	426 (4.58)
8					263 (4.49)		448 (4.32)
9					280 (4.18)	324 (4.15)	430 (4.55)
10					283 (4.56)	327 (4.46)	403 (4.83)
11					283 (4.05)	333 (3.86)	435 (4.41)
12					272 (4.20)	318 (4.00)	427 (4.43)
13					313 (4.41)	364 (4.15)	425 (4.27)
14					286 (4.68)		403 (4.58)
15				230 (4.59)	282 (4.43)	326 (3.96)	445 (4.19)

[a] M.p. 247–250°; ref. 4 gives 261–262° for *cis* isomer, 262–263° for *trans*; principal absorption maxima in MeOH at 348 mμ for *cis* and 423 for *trans*. [b] M.p. 284–286°; ref. 4 gives 281–282° and maxima at 263 and 307 mμ for *cis* isomer; 356 mμ for *trans* isomer. [c] M.p. 222°. [d] M.p. 193–196°. [e] Numbers refer to compounds in Table I. [s] Shoulder.

without the use of acetic anhydride.[3] This implies the same configuration for all, and on the basis of the infrared spectra the structures must be *trans*.

Only two notes concerning *cis-trans* isomerism in the styrylquinolines have been previously published,[4,5] and in both papers configurations were assigned not to the free styrylquinolines but only to quaternary bases obtained from them *via* reaction with dimethyl sulfate or methyl iodide. Reportedly only *cis* structures were obtained by this route, and Horwitz[4] has stated that aldehyde condensations with quinaldine in acetic anhydride appear to require a mechanism similar to that of the Chugaev reaction and thus permit only a *cis* product. However, in the closely related stilbazole series Horwitz[6] could obtain only the *trans* isomers in 10 of 12 examples tried, and in one of the other two trials prolonged refluxing with acetic anhydride produced conversion to the *trans* isomer. Condensation of 1-ethylquinaldinium iodide with vanillin[5] in the presence of acetic anhydride gives only the *trans* isomer. It is therefore rather doubtful that acetic anhydride exerts any special favoritism to the production of *cis* compounds.

Since Horwitz has published only the "principal" absorption maxima of his *cis*-styrylquinolinium methosulfates, direct comparison to our spectra (on the plausible assumption that the hydrochlorides should have spectra essentially similar to the methosulfates except for the relatively minor shifts due to different substituents) proved useless, demonstrating only that our spectra were much different from those of the *cis*-methosulfates.

For a more direct comparison piperonal was condensed with quinaldine and 6-ethoxyquinaldine, yielding the same styrylquinolines previously reported,[4] and the spectra of these in acidic ethanol were determined (Table II). While the piperonal-quinaldine derivative has a spectrum similar to that previously reported for the *trans*-methosulfate prepared by a different route, the 6-ethoxyquinaldine derivative not only shows approximately the same "principal" maxima stated for the *cis*-methosulfate but an additional and unreported strong band at 421 mμ., a longer wave length than any listed for the putative *trans*-methosulfate. By treating the free bases with methyl sulfate according to Horwitz's procedure we obtained methosulfates with spectra quite similar to those of the hydrochlorides, and very substantially in disagreement with Horwitz's data for the *cis* isomers.

Similar repetition of the vanillin-quinaldine condensation[5] also yielded in our hands a hydrochloride and methosulfate having a *trans* rather than *cis* spectrum. The methosulfate formed a phenol betaine by treatment with aqueous alkali, although this has been reported[5] to occur only with the *cis* iodide and not the *trans*. (However, our compound

(3) J. P. Phillips, W. Huber, J. Chung, and L. L. Merritt, *J. Am. Chem. Soc.*, **73**, 630 (1951).

(4) L. Horwitz, *J. Am. Chem. Soc.*, **77**, 1687 (1955).

(5) M. Ito and K. Matsumura, *J. Org. Chem.*, **21**, 1039 (1956).

(6) L. Horwitz, *J. Org. Chem.*, **21**, 1039 (1956).

was a methosulfate, prepared according to Horwitz, and not the methiodide.) This phenol betaine shows the characteristic and very striking color variations with solvent[7]: in acid, yellow; in alcoholic alkali blue; in aqueous alkali, red to purple.

EXPERIMENTAL

Preparation of compounds. The general procedure for synthesis of the 2-styryl-8-hydroxyquinolines is as follows. 8-Hydroxyquinaldine (3.2 g.) is mixed with an equivalent amount of the aromatic aldehyde and 5 ml. acetic anhydride added. The mixture is refluxed 4–6 hr., then poured into water and neutralized with 10% sodium hydroxide solution. The precipitate is filtered, washed with 5% sodium bicarbonate and water, and then heated 1 hr. with 50 ml. 10% sodium hydroxide to hydrolyze the acetate. After neutralization with hydrochloric acid the product is filtered, washed with sodium bicarbonate and water, and recrystallized from ethanol. Since there are usually appreciable impurities at this point, the compound is dissolved in hot ethanol and 3–5 ml. concentrated hydrochloric acid added. A bulky precipitate of the hydrochloride forms quickly and this is recrystallized once or twice from ethanol containing hydrochloric acid.

Compounds 4 and 8 in Table I were similarly prepared from 8-hydroxylepidine, and compound 6 from 8-methoxyquinaldine. An attempt to condense chloral with 8-hydroxyquinaldine produced only extensive decomposition.

All melting points were taken on a Kofler hot stage, and are within a two-degree range of the values in Table I except as noted there. All the hydrochlorides melted with decomposition, and several were observed to sublime from the top of the slide to the cover glass well below the melting point. Melting points for free bases corresponding to some of the hydrochlorides of Table I are as follows: compound 3, 86°; 4, 150°; 5, 215°; 8, 153°; 9, 131°; and 13, 132°. These free bases were obtained by neutralizing the hydrochloride followed by recrystallization from ethanol. No differences in properties of the free bases before and after hydrochloride formation were observed other than minor melting point variations.

The styrylquinolines and methosulfates from quinaldine or 6-ethoxyquinaldine and piperonal were prepared according to the literature.[4] Melting points of the free bases agreed with published values within two degrees. Condensation of quinaldine with vanillin[5] also gave the same free base previously reported; quaternization was performed by Horwitz's method with dimethyl sulfate.

Spectra. All ultraviolet and visible spectra were recorded with a Beckman DK Spectrophotometer in ethanol 0.1*M* in hydrochloric acid, except the methosulfates which were run in ethanol alone. Concentrations ranged from 1 to 4 × $10^{-5}M$.

Infrared spectra were determined by the potassium bromide pellet technique on a Baird AB-2 Spectrophotometer in the range 2–16 μ.

Acknowledgment. This work was supported by a grant (NSF G5447) from the National Science Foundation. The DK Spectrophotometer was also supplied by an NSF grant (G4074).

LOUISVILLE, KY.

(7) S. Hünig and O. Rosenthal, *Ann.*, **592**, 161 (1955).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF CONNECTICUT]

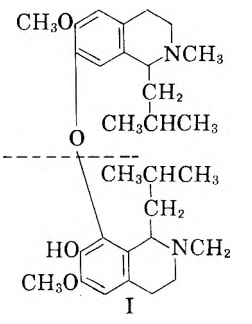
Synthesis of Isoquinoline Alkaloids. I. Lophocerine[1]

J. M. BOBBITT AND TSU-TEH CHOU[2]

Received February 18, 1959

The cactus alkaloid lophocerine (1-isobutyl-2-methyl-6-methoxy-7-hydroxy-12,3,4-tetrahydroisoquinoline) which can be isolated from *Lophocereus Schottii* as its methyl ether has been synthesized.

Three alkaloids have been isolated from the giant cactus *Lophocereus Schottii* by Djerassi and his coworkers. Two of these alkaloids, pilocereine[3–5] and piloceredine[6] (diastereoisomers of I) could be considered *dimeric* since they contain two isoquinoline residues. When the phenolic alkaloidal fraction



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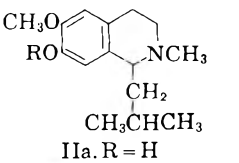


IIa. R = H
IIb. R = CH_3
IIc. R = $CH_2\phi$
IId. R = CH_2CH_3

from *L. Schottii* was distilled and methylated, a third compound was isolated and shown to be 1-isobutyl-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (IIb).[6] It was suggested that this methyl ether represented a *monomeric* alkaloid to be called lophocerine. The free phenol group was assigned to the 7-position (structure IIa) by anal-

(1) This investigation was supported in part by Research Grant CY-3905 from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service.

(2) Abstracted from the M.S. thesis of Tsu-teh Chou, The University of Connecticut, 1959. Present address: Institute of Materia Medica, Academia Sinica, Shanghai, China.

(3) G. Heyl, *Arch. Pharm.*, **239**, 451 (1901).

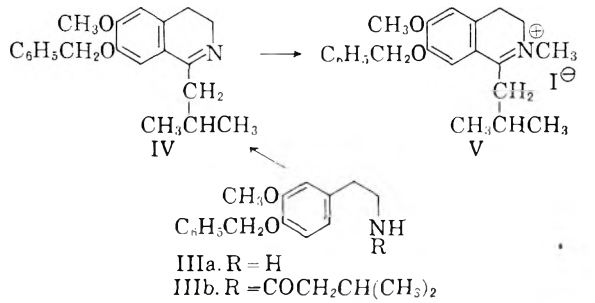
(4) C. Djerassi, N. Frick, and L. E. Geller, *J. Am. Chem. Soc.*, **75**, 3632 (1953).

(5) C. Djerassi, S. K. Figdor, J. M. Bobbitt, and F. X. Markley, *J. Am. Chem. Soc.*, **78**, 3861 (1956); **79**, 2203 (1957).

(6) C. Djerassi, T. Nakano, and J. M. Bobbitt, *Tetrahedron*, **2**, 58 (1958).

ogy with other cactus alkaloids[7] and biogenetic reasoning.[8] It was also noted[6] that the dimeric alkaloids might be formed in the plant by the oxidative coupling[8] of two molecules of lophocerine (dotted line in I). Lophocerine, IIa, has now been synthesized.

Vanillin was benzylated[9] and the resulting 3-methoxy-4-benzyloxybenzaldehyde (85%) was condensed with nitromethane[10] to yield 3-methoxy-4-benzyloxy-ω-nitrostyrene[11] (81%). The nitrostyrene was reduced with lithium aluminum hydride to yield 2-(3-methoxy-4-benzyloxyphenyl)ethylamine, IIIa (80.2%, isolated as hydrohcloride[11]). A good yield of amine was obtained only when the reaction mixture was hydrolyzed by the elegant method of



Amundsen and Nelson.[12] In general, the amine was converted, without isolation, to *N*-[2-(3-methoxy-4-benzyloxyphenyl)ethyl] isovaleryl amide, IIIb, (81.5% from nitrostyrene) by reaction with isovaleryl chloride in the presence of an anhydrous anion exchange resin (Amberlite IRA-400). The resin was found to be more convenient than the conventional bases, sodium hydroxide, and calcium hydroxide. The amine hydrochloride could also be converted directly to the amide by a resin technique.

N-[2-(3-methoxy-4-benzyloxyphenyl)ethyl] isovaleryl amide, IIIb, was converted to 1-isobutyl-6-methoxy-7-benzyloxy-3,4-dihydroisoquinoline, IV (57%, isolated and characterized as a picrate) with phosphorus pentachloride.[13] The dihydroisoquinoline, IV, was regenerated from its picrate with the modified anion exchange resin Amberlite IRA-400-HCO_3[14] and converted, without isolation, to the methiodide, V (97% from picrate). The methiodide was hydrogenated with Adams catalyst and passed over Amberlite IRA-400-HCO_3[14] (to remove hydriodic acid) to yield benzyllophocerine, IIc (1 - isobutyl - 2 - methyl - 6 - methoxy - 7-benzyloxy-1,2,3,4-tetrahydroisoquinoline, 91.3%). Benzyllophocerine was not crystalline but was characterized by a picrate and a styphnate. The methiodide, V, was hydrogenated with Adams catalyst, passed over Amberlite IRA-400-HCO_3 and again hydrogenated with palladium on charcoal to yield lophocerine, IIa (90%). No conditions were found for carrying out both reductions simultaneously. Lophocerine was also not crystalline but was characterized by a picrate and a styphnate.

The structure of synthetic lophocerine was further established by methylation (diazomethane) and ethylation (diazoethane) to the methyl, IIb, and ethyl, IId, ethers. The respective picrates and styphnates of these ethers were identical with authentic specimens.[15]

EXPERIMENTAL

The melting points were determined on a Kofler Hot Stage melting point apparatus and are corrected. The vanillin used was contributed by the Dow Chemical Company of Midland, Mich. Unless noted, all other chemicals were commercial materials used without purification. The microanalyses were performed by Geller Laboratories, Bardonia, N. Y.

2-(3-Methoxy-4-benzyloxyphenyl)ethylamine, IIIa (hydrochloride). 3-Methoxy-4-benzyloxy-ω-nitrostyrene[10,11] (28.5 g., 0.1 mole) was placed in the thimble of a Soxhlet extractor and washed gradually (30 hr.) into 500 ml. of stirred, refluxing, anhydrous ether containing 19.0 g. (0.5 mole) of lithium aluminum hydride. The mixture was cooled in an ice bath and stirred vigorously during the successive addition of 10 ml. of water, 8 ml. of 20% aqueous sodium hydroxide and 37 ml. more of water. The mixture was stirred for 15 min., the ether layer was decanted and the residue was washed three times with ether. The combined decantate and washings were dried over potassium hydroxide, again decanted, and saturated with anhydrous hydrogen chloride. The white crystalline hydrochloride was recrystallized from ethanol to yield 23.5 g. (80.2%) of product, m.p. 176–178° (rec. 173–175°[11]).

N-[2-(3-Methoxy-4-benzyloxyphenyl)ethyl]isovaleryl amide, IIIb. The dried ether solution containing the amine, IIIa, described above was diluted to 1500 ml. with ether, combined with 80 g. (about 0.2 equiv.) of dry Amberlite IRA-400[16] and vigorously stirred during the dropwise addition of 18.3 ml. (18 g., 0.15 mole) of isovaleryl chloride. The mixture was stirred under reflux until the white precipitate, which formed immediately, was dissolved (24 hr.). The resin was separated by filtration and the filtrate was washed with 2*N* sodium hydroxide, 2*N* hydrochloric acid and dried over sodium sulfate. On evaporation, 27.8 g. (81.5% from the nitrostyrene) of amide, m.p. 111–114° was obtained. The m.p.

(7) L. Reti in R. H. F. Manske and H. L. Holmes, *The Alkaloids*, Vol. IV, Academic Press, New York, 1954, pp. 7–28.

(8) R. Robinson, *The Structural Relations of Natural Products*, Oxford University Press, London, 1955, p. 85; R. H. F. Manske, ref. 7, p. 1.

(9) R. Dickinson, I. M. Heilbron, and F. Irving, *J. Chem. Soc.*, 1888 (1927).

(10) K. H. Slotta and G. Szyszka, *J. prakt. Chem.*, **137**, 339 (1933); *Chem. Abstr.*, **57**, 4221 (1933).

(11) S. Kobayashi, *Sci. Papers Inst. Phys. Chem. Research (Tokyo)*, **6**, 149 (1927); *Chem. Abstr.*, **22**, 1345 (1928).

(12) L. H. Amundsen and L. S. Nelson, *J. Am. Chem. Soc.*, **73**, 242 (1951).

(13) R. Robinson and S. Sugasawa, *J. Chem. Soc.*, 280 (1933).

(14) J. M. Bobbitt, *J. Org. Chem.*, **22**, 1729 (1957).

(15) (a) C. Djerassi, F. X. Markley, and R. Ehrlich, *J. Org. Chem.*, **21**, 975 (1956); (b) C. Djerassi, J. J. Beereboom, S. P. Marfey, and S. K. Figdor, *J. Am. Chem. Soc.*, **77**, 484 (1955). We are indebted to Professor Djerassi for authentic samples of these compounds.

(16) This resin was donated by the Rohm and Haas Company, Philadelphia, Pa. It was regenerated to its basic form with 4% sodium hydroxide, washed with water followed by methanol and dried over calcium chloride under vacuum for 12–14 hr.

was 114–115° after one recrystallization from hexane-benzene.

Anal. Calcd. for $C_{21}H_{27}NO_3$: C, 73.9; H, 8.0; N, 4.1. Found: C, 73.9; H, 8.0; N, 4.2.

1-Isobutyl-6-methoxy-7-benzyloxy-3,4-dihydroisoquinoline, IV (*picrate*). A solution of 6.84 g. (0.02 mole) of *N*-[2-(3-methoxy-4-benzyloxyphenyl)ethyl] isovaleryl amide, IIIb, in 100 ml. of dry chloroform was added slowly to a stirred and cooled (ice bath) suspension of 30 g. (0.145 mole) of phosphorus pentachloride in 160 ml. of the same solvent. The mixture was stirred at 0° for 1 hr. and allowed to stand at 5° overnight and at 25° for 3 days. Crushed ice (600 g.) was added with stirring and 5 ml. of methanol was added to break the emulsion. The separated chloroform layer was evaporated to a dark oil and treated with 5.6 g. (0.024 mole) of picric acid in 100 ml. of ethanol. The mixture was warmed and then cooled to deposit 7.12 g. of crude picrate which was recrystallized from benzene to give 6.28 g. (57%) of dihydroisoquinoline picrate, m.p. 170–171°. Three recrystallizations from benzene yielded the analytical sample, m.p. 171–172°.

Anal. Calcd. for $C_{27}H_{28}N_4O_9$: C, 58.7; H, 5.1; N, 10.1. Found: C, 58.7; H, 5.2; N, 10.2.

1-Isobutyl-2-methyl-6-methoxy-7-benzyloxy-3,4-dihydroisoquinoline methiodide, V. 1-Isobutyl-2-methyl-6-methoxy-7-benzyloxy-3,4-dihydroisoquinoline picrate (0.55 g., 0.001 mole) was dissolved in 50 ml. of 6% aqueous acetone and poured slowly over a column of Amberlite IRA-400-HCO_3[14] (25 ml.) previously washed with the same solvent. The column was washed with an additional 50 ml. of solvent, and the eluents were concentrated in vacuum to about 20 ml. and extracted with 50 ml. of benzene. Excess methyl iodide (1.2 ml., 2.7 g.) was added and, after 2 days, the solution deposited 0.45 g. (97%) of methiodide, V, m.p. 208–211°. Three recrystallizations from ethanol yielded the analytical sample, m.p. 209–211°.

Anal. Calcd. for $C_{22}H_{28}INO_2$: C, 56.8; H, 6.1; I, 27.3; N, 3.0. Found: C, 56.7; H, 6.2; I, 27.0; N, 3.0.

Benzyllophocerine (*1-isobutyl-2-methyl-6-methoxy-7-benzyloxy-1,2,3,4-tetrahydroisoquinoline*) IIc. One gram (0.022 mole) of methiodide, V, dissolved in 35 ml. of methanol was hydrogenated (48 p.s.i., 25°) in the presence of 0.1 g. of Adams catalyst. After 3 hr. the catalyst was removed by filtration; the solution was passed over 20 ml. of IRA-400-HCO_3[14] (previously washed with methanol) and the solvent was evaporated under vacuum to yield 0.68 g. (91.3%) of a faint yellow oil. The analytical sample was sublimed (152°, 0.5 mm.).

Anal. Calcd. for $C_{22}H_{29}NO_2$: C, 77.8; H, 8.6; N, 4.1. Found: C, 77.4; H, 8.7; N, 4.3.

A *picrate* was prepared in absolute ethanol and recrystallized twice from the same solvent to give the analytical sample, m.p. 151–152°.

Anal. Calcd. for $C_{28}H_{32}N_4O_9$: C, 59.1; H, 5.7; N, 9.9. Found: C, 59.4; H, 5.9; N, 9.8.

A *styphnate* was prepared in absolute ethanol, m.p. 138–141°,[17] and recrystallized twice from the same solvent to give an analytical sample, m.p. 151.5–153°.

Anal. Calcd. for $C_{28}H_{32}N_4O_{10}$: C, 57.5; H, 5.5; N, 9.6. Found: C, 57.8; H, 5.8; N, 9.6.

Lophocerine (*1-isobutyl-2-methyl-6-methoxy-7-hydroxy-1,2,3,4-tetrahydroisoquinoline*, IIa. Benzyllophocerine, IIc, in methanol (100 ml.) was prepared as described above from 3.0 g. (0.0065 mole) of methiodide, V, and again hydrogenated (45 p.s.i., 25°) over 0.2 g. of 5% palladium-on-charcoal. After 3 hr., the catalyst was removed by filtration and the filtrate was evaporated under vacuum to yield 1.46 g. (90%) of heavy orange oil which gave a purple coloration with ferric chloride. The analytical sample was sublimed (96–104°, 0.5 mm.).

Anal. Calcd. for $C_{15}H_{23}NO_2$: C, 72.2; H, 9.3; N, 5.6. Found: C, 72.2; H, 9.4; N, 5.7.

A *picrate* was prepared in benzene, m.p. 172–175°,[17] and recrystallized twice from the same solvent to give the analytical sample, m.p. 191.5–193°.

Anal. Calcd. for $C_{21}H_{26}N_4O_9$: C, 52.7; H, 5.5; N, 11.7. Found: C, 52.7; H, 5.4; N, 12.0.

A *styphnate* was prepared in absolute alcohol and recrystallized six times from the same solvent to give the analytical sample, m.p. 171–172°.

Anal. Calcd. for $C_{21}H_{26}N_4O_{10}$: C, 51.0; H, 5.3; N, 11.3. Found: C, 51.3; H, 5.3; N, 11.4.

Lophocerine methyl ether, IIb, *and lophocerine ethyl ether*, IId. Lophocerine was methylated in 50% methanolic ether at 5° with excess diazomethane prepared from the di(*N*-nitroso-*N*-methylamide) of terephthalic acid[18] by distillation.[19] After 40 hr., the excess diazomethane was evaporated, additional ether was added, and the resulting ether-methanol was washed with 2*N* sodium hydroxide, dried over sodium sulfate, and evaporated. One portion was treated with picric acid in ethanol to give a picrate, m.p. 180–182° (rec.[15b] 183–185°) and the other portion was treated with styphnic acid in ethanolic to give a styphnate, m.p. 210–212° (rec.[15b] 212–214°). Mixture melting points with authentic samples were undepressed.

Lophocerine was ethylated at 25° with excess diazoethane prepared by distillation[19] from *N*-ethyl-*N*-nitrosourea.[20] After seven days the reaction mixture was treated as described above to yield a picrate, m.p. 150–153° (rec.[15a] 153–153.5°) and a styphnate, m.p. 182–183° (rec.[15a] 183–184°). Mixture melting points with authentic specimens were undepressed.

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(17) Because of its sharpness, this might represent a crystalline modification. The high melting form could not be converted to the low melting form.

(18) This compound was donated by the Explosives Division of E. I. du Pont de Nemours Co. of Wilmington who sell it as EXR-101.

(19) F. Arndt, *Org. Syntheses*, **Coll. Vol. II**, 165 (1943).

(20) Prepared by the procedure given in A. I. Vogel, *Practical Organic Chemistry*, 3rd ed., Longmans Green, London, 1956, p. 969, for *N*-nitroso-*N*-methylurea.

[CONTRIBUTION FROM THE DIVISION OF CHEMICAL RESEARCH OF G. D. SEARLE & CO.]

Steroidal Aldosterone Blockers. II[1]

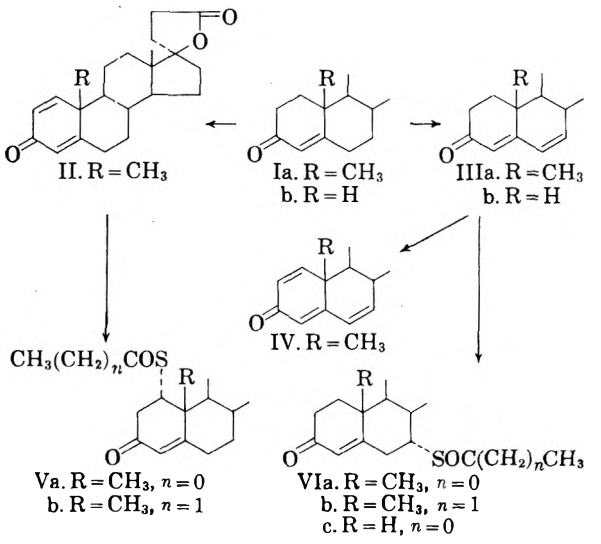
JOHN A. CELLA AND ROBERT C. TWEIT

Received February 20, 1959

The synthesis and biological activities of several new steroidal 17-spirolactones are presented. Introduction of unsaturation and the acylthio grouping enhances oral aldosterone blocking activity in this series of compounds.

The first series of steroidal spirolactones which were reported[1] showed much better aldosterone blocking activities when administered parenterally than when given orally. This report deals with a group of related steroids which show good activities when taken by mouth.

In casting about for modifications of the compounds reported earlier we decided to introduce unsaturation at the C-1 and C-6 centers of Ia because of the desirable effects produced by such changes in some biologically active steroids.[2] Reaction of Ia with selenious acid[3] produced the corresponding $\Delta^{1,4}$-3-oxo-derivative (II). On the other hand when Ia was treated with chloranil[4] the corresponding $\Delta^{4,6}$-3-oxo-steroid (IIIa) was formed. We were able to prepare the $\Delta^{4,6}$-3-oxo-compound (IIIb) from Ib with chloranil,[3] although in poor yield. The $\Delta^{1,4,6}$-3-oxo-derivative (IV) of Ia was prepared by treatment of IIIa with selenious acid.



We found that these dehydrogenated derivatives all possessed enhanced oral activity. Encouraged, we then set about to make the alkanethiolic acid adducts of these compounds on the chance of obtaining higher activities, since the 7α-acetylthio derivative of 17α-hydroxyprogesterone was found to be more potent than the parent compound when administered parenterally.

As we expected[5] ethanethiolic acid and propanethiolic acid added readily to either the 1,2 or the 6,7 double bond. Treatment of II with ethanethiolic acid gave the 1α-acetylthio compound (Va); propanethiolic acid yielded the 1α-propionylthio derivative (Vb). Heating the $\Delta^{4,6}$-3-oxo steroid (IIIa) with ethanethiolic or propanethiolic acid produced the corresponding 7α-acetylthio (VIa) and 7α-propionylthio (VIb) compounds, respectively. The 19-nor analog (IIIb) yielded the 7α-acetylthio compound (VIc) when allowed to react with ethanethiolic acid. The assignment of position as well as configuration of the acylthio substituents mentioned above was made by analogy to the work reported by Dodson and Tweit[5] on similar additions.

The aldosterone blocking potency[6] of most of these compounds is recorded in Table I. The most potent compound when administered orally is VIa. This result was unexpected since VIa failed to

TABLE I

ALDOSTERONE BLOCKING POTENCIES[6]

Compound	M.E.D.[a]	Compound	M.E.D.[a]
Ia	21	IV	0.9
Ib	1.6	Va	>0.8
II	1.5	VIa	0.4
IIIa	1.1	VIb	0.6

[a] M.E.D. is the minimal effective dose in mg. which produces a 50% block of the effect of 12 μg. desoxycorticosterone on the urinary sodium-potassium ratio of adrenalectomized rats, when the test compound is administered orally.

(1) For previous papers in this area see (a) J. A. Cella and C. M. Kagawa, *J. Am. Chem. Soc.*, **79**, 4808 (1957), and (b) J. A. Cella, E. A. Brown, and R. R. Burtner, *J. Org. Chem.*, **24**, 743 (1959).

(2) For example, see H. L. Herzog, A. Nobile, S. Tolksdorf, W. Charney, E. B. Hershberg, P. L. Perlman, and M. M. Pechet, *Science*, **121**, 176 (1955).

(3) C. Meystre, H. Frey, W. Voser, and A. Wettstein, *Helv. Chim. Acta*, **39**, 734 (1956); S. A. Szpilfogel, T. A. P. Posthumus, M. S. de Winter, and D. A. Van Dorp, *Rec. trav. chim.*, **75**, 475 (1956).

(4) E. J. Agnello and G. D. Laubach, *J. Am. Chem. Soc.*, **79**, 1257 (1957).

(5) R. M. Dodson and R. C. Tweit, *J. Am. Chem. Soc.*, **81**, 1224 (1959).

(6) The aldosterone blocking activities were determined by Dr. C. M. Kagawa and his associates of these laboratories. The assay involves the use of desoxycorticosterone as the sodium retainer and results are related to aldosterone by analogy. The details of this test method have been published: C. M. Kagawa, J. A. Cella, and C. G. Van Arman, *Science*, **126**, 1015 (1957). The results reported here will be published elsewhere in detail.

show improved activity over Ia when administered parenterally.

EXPERIMENTAL

We are indebted to Dr. R. T. Dillon and his staff of the Analytical Division of G. D. Searle and Co. for all microanalyses and optical determinations. All melting points were determined on a Fisher-Johns hot stage melting point apparatus and are uncorrected. Ultraviolet spectra were determined in methanol. Optical rotations were measured in chloroform except as otherwise noted.

3-(3-Oxo-17β-hydroxy-1,4-androstadien-17α-yl)propanoic acid lactone (II).[7] To a solution of 50 g. of Ia[1] and 1.0 g. of mercuric chloride in 3 l. of *t*-butyl alcohol and 30 ml. of acetic acid, 17.8 g. of selenious acid was added with stirring. After the mixture had been refluxed under nitrogen for 8 hr., a second portion of 17.8 g. of selenious acid was added and the reflux period continued for an additional 13 hr. The *t*-butyl alcohol solution was filtered and concentrated, the residue was dissolved in methylene chloride and the solution was washed with 2% sodium hydroxide and ammonium sulfide solutions. Then the organic layer was washed with water, dried, and concentrated to dryness leaving a crystalline residue which was recrystallized twice from ethyl acetate to yield 16.3 g. of II, m.p. 179–180° (another form melts 134–136°), $[\alpha]_D$ +22° (diox), ϵ^{245} 14,900.

Anal. Calcd. for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29. Found: C, 77.34; H, 8.28.

3-(3-Oxo-17β-hydroxy-4,6-androstadien-17α-yl)propanoic acid lactone (IIIa). A solution of 2.5 g. of Ia,[1] 2.5 g. of chloranil and 0.025 g. of *p*-toluenesulfonic acid hydrate in 250 ml. of xylene was heated at reflux for 20 hr. The mixture was cooled and filtered and the solvent was removed by vacuum distillation. The residue was taken up in benzene and chromatographed over 250 g. of silica using benzene and ethyl acetate as developing solvents. The 15% ethyl acetate 85% benzene eluate yielded a solid which on recrystallization from ethyl acetate gave 0.65 g. of diene IIIa, m.p.146–151° (remelts 165°). Recrystallization of this product from ethyl acetate yielded 0.44 g. of IIIa, m.p. 149–151°, $[\alpha]_D$ +24.5°, ϵ^{283} 26,700.

Anal. Calcd. for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29. Found: C, 77.65; H, 8.54.

3-(3-Oxo-17β-hydroxy-19-nor-4,6-androstadien-17α-yl)-propanoic acid lactone (IIIb). A solution of 4.05 g. of Ib,[1] 3.34 g. of chloranil, and 0.01 g. of *p*-toluenesulfonic acid monohydrate in 400 ml. of xylene was heated under reflux for 1 hr. and then the xylene was removed under vacuum The residue was dissolved in benzene and chromatographed on 560 g. of silica gel. The column was washed with benzene and 5%, 10%, and 15% ethyl acetate in benzene. The product was eluted with liter portions of 20% ethyl acetate in benzene. The residues from the fourth and fifth liters of eluate were crystallized twice from ethyl acetate to yield 0.26 g. of IIIb, m.p. 235–239°, $[\alpha]_D$ −44°, ϵ^{283} 27,000.

Anal. Calcd. for $C_{21}H_{26}O_3$: C, 77.26; H, 8.03. Found: C, 76.97; H, 8.31.

3-(3-Oxo-17β-hydroxy-1,4,6-androstatrien-17α-yl)propanoic acid lactone (IV). According to the procedure described by Agnello and Laubach,[4] 0.34 g. of 4,6-diene IIIa was treated with a total of 0.155 g. of selenious acid in two portions in 50 ml. of *t*-butyl alcohol containing 0.5 ml. of acetic acid. The product was chromatographed over silica using benzene and ethyl acetate as developing solvents. The eluate composed of 15% ethyl acetate contained 0.181 g. and could be crystallized from methanol to give 0.05 g. of the 1,4,6-triene IV, as the monomethanolate, m.p. 97–100° (dec., remelts 136–138°), $[\alpha]_D$ 0°, ϵ^{222} 11,100, ϵ^{256} 10,700, ϵ^{296} 13,700.

Anal. Calcd. for $C_{22}H_{28}O_3 \cdot CH_3OH$: C, 74.56; H, 8.16. Found: C, 74.88; H, 8.09.

A second crop of material weighed 0.05 g. and melted 95–98° (dec.).

3-(3-Oxo-1α-acetylthio-17β-hydroxy-4-androsten-17α-yl)-propanoic acid lactone (Va). A solution of 1.0 g. of II in 1 ml. of ethanethiolic acid was heated on the steam bath for 0.5 hr. Part of the excess thiolic acid was then evaporated under nitrogen and the residue was dissolved in a mixture of ethyl acetate–ether. On scratching, crystals formed and these were separated by filtration and recrystallized from ethyl acetate to yield 0.40 g. of Va, m.p. 199–200° (dec.), $[\alpha]_D$ +56°, $\epsilon^{240.5}$ 16,200.

Anal. Calcd. for $C_{24}H_{32}O_4S$: C, 69.20; H, 7.74. Found: C, 69.15; H, 7.84.

Additional fractions melting at 194–196° and 198–199° were obtained to bring the total yield to 0.75 g. (61%).

3-(3-Oxo-1α-propionylthio-17β-hydroxy-4-androsten-17α-yl)propanoic acid lactone (Vb). A solution of 0.35 g. of II in 0.5 ml. of propanethiolic acid was heated on a steam bath for 1.25 hr. Ethyl acetate and Skellysolve B were added and the solution allowed to stand overnight. The crystals which formed were recrystallized from a benzene–Skellysolve B mixture. There was obtained 0.08 g. of Vb, m.p. 176–178° (dec.), $\epsilon^{240.5}$ 16,500.

Anal. Calcd. for $C_{25}H_{34}O_4S$: C, 69.73; H, 7.96. Found: C, 69.81; H, 8.13.

3-(3-Oxo-7α-acetylthio-17β-hydroxy-4-androsten-17α-yl)-propanoic acid lactone (VIa). A solution of 0.75 g. of IIIa in 0.75 ml. of ethanethiolic acid was heated on a steam bath for 1 hr. Most of the excess solvent was removed in a stream of dry nitrogen. Crystallization of the oily residue from methanol yielded 0.65 g. of VIa, m.p. 130–135°. Recrystallization yielded 0.45 g., m.p. 134–135° (resolidified and remelted 201–202° dec.), $[\alpha]_D$ −33.5°, ϵ^{238} 20,200.

Anal. Calcd. for $C_{24}H_{32}O_4S$: C, 69.20; H, 7.74. Found: C, 69.25; H, 7.75.

3-(3-Oxo-7α-propionylthio-17β-hydroxy-4-androsten-17α-yl)propanoic acid lactone (VIb). A solution of 0.65 g. of IIIa in 0.5 ml. of propanethiolic acid was heated on the steam bath for 0.5 hr. Most of the excess thiolic acid was removed under vacuum and on trituration with methanol crystals of VIb formed, 0.34 g., m.p. 192–194° (dec.), $[\alpha]_D$ −37°, ϵ^{238} 19,800.

Anal. Calcd. for $C_{25}H_{34}O_4S$: C, 69.73; H, 7.96. Found: C, 69.86; H, 8.10.

3-(3-Oxo-7α-acetylthio-17β-hydroxy-19-nor-4-androsten-17α-yl)propanoic acid lactone (VIc). One hundred seventy mg. of IIIb was dissolved in 0.5 ml. of ethanethiolic acid and heated on a steam bath for 1.5 hr. Most of the excess thiolic acid was removed under vacuum and methanol was added. On scratching 87 mg. of crystals of VIc formed, m.p. 111–113°, ϵ^{237} 21,000.

Anal. Calcd. for $C_{23}H_{30}O_4S$: C, 68.62; H, 7.51. Found: C, 68.30; H, 7.54.

CHICAGO 80, ILL.

(7) We are indebted to Mr. Richard Gueldner for technical assistance in this preparation.

[CONTRIBUTION FROM THE ROHM & HAAS CO.]

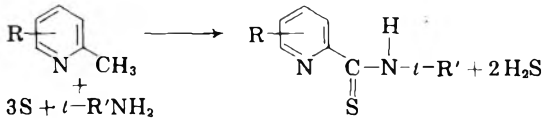
Preparation of Some *N*-*t*-Alkylthiopicolinamides

RICHARD C. MANSFIELD

Received February 26, 1959

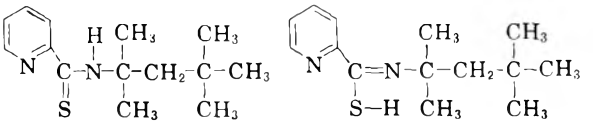
N-*t*-Alkylthiopicolinamides have been obtained from the reaction of *t*-carbinamines with sulfur and α-picoline. 2,3-Lutidine, 2,4-lutidine, 2,6-lutidine, and 2-methyl-5-ethylpyridine react with sulfur and *t*-carbinamines only at the 2-methyl group to give *N*-*t*-alkylthiopicolinamides.

A general investigation of some reactions of *t*-carbinamines and reports that methyl pyridines undergo reactions with sulfur and aromatic amines[1-6] and with sulfur and morpholine[1] prompted an investigation of the reaction of *t*-carbinamines and sulfur with α-picoline and a number of monosubstituted α-picolines.



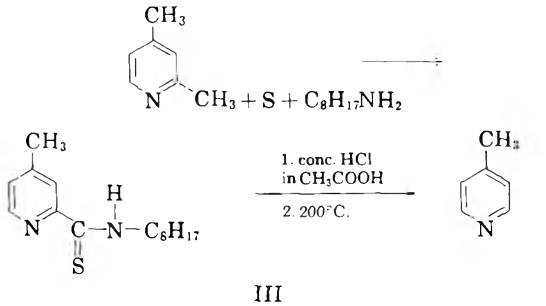
R = H, 3-CH_3, 4-CH_3, 6-CH_3, or 5-CH_2CH_3
R′ = *t*-butyl, *t*-octyl, *t*-$C_{11-14}H_{23-29}$, *t*-$C_{18-22}H_{37-45}$

The reaction of α-picoline, sulfur, and *t*-octylamine gave a good yield of *N*-*t*-octylthiopicolinamide (I). The infrared spectrum indicated that this material exists only in the thione tautomeric form. There was an intense band at 3325 cm.$^{-1}$ which can be attributed to the N—H stretching vibration. Strong absorption near 1470 cm.$^{-1}$ was attributed to the —N—C=S group. Absorption in the 2550–2600 cm.$^{-1}$ region from the S—H stretching vibration of the thioenol tautomeric form (II) was not observed.



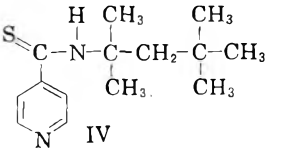
I II

Reaction of *t*-octylamine and sulfur with 2,4-lutidine occurred only at the 2-methyl group to give *N*-(*t*-octyl)-4-methylthiopicolinamide (III). Hydrolysis of III, followed by decarboxylation gave only 4-methylpyridine. No 2-methylpyridine, which would have resulted if reaction had occurred at the 4-methyl group, was obtained. The thioamide (III) absorbed strongly at 832 cm.$^{-1}$, which is to be



III

expected for a 2,4-substituted pyridine. In addition, the spectra of III and I showed many points of similarity not shared by the spectrum of *N*-*t*-octylthioisonicotinamide (IV).

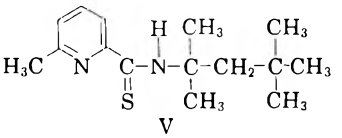


IV

Lochte and Cheavens[7] have shown preferential reaction at the 4-methyl group in the methyl iodide alkylation of 2,4-lutidine using the sodamide-liquid ammonia method. The participation of 2- and 4-methylpyridine in certain ionic reactions has been explained by resonance stabilization of the carbanions,[8] and the greater reactivity of the 4-isomer has been attributed to its enhanced ability to participate in hyperconjugation involving the more important *p*-quinoid structures.[7-9] Pryor[10] has postulated that sulfur plus any nucleophile gives polysulfides which undergo fission to yield radicals capable of abstracting benzyl hydrogens. It is possible, therefore, that the initial step in reactions of methyl pyridines with sulfur and amines is abstraction of a picolyl hydrogen by an amine polysulfide, since this would not necessarily imply preferential reaction at the 4-methyl group of 2,4-lutidine. In fact, Porter[1] has observed that 2-methylpyridine reacted more readily with sulfur and aniline than did 4-methylpyridine.

(1) H. D. Porter, *J. Am. Chem. Soc.*, **76**, 127 (1954).
(2) B. Emmert and M. Groll, *Ber.*, **86**, 208 (1953).
(3) B. Emmert and A. Holz, *Ber.*, **87**, 676 (1954).
(4) K. V. Martin, *J. Am. Chem. Soc.*, **80**, 233 (1958).
(5) F. Lions and K. V. Martin, *J. Am. Chem. Soc.*, **80**, 1591 (1958).
(6) P. E. Miller, G. L. Oliver, J. R. Dann, and J. W. Gates, Jr., *J. Org. Chem.*, 22, 664 (1957).
(7) H. L. Lochte and T. H. Cheavens, *J. Am. Chem. Soc.*, **79**, 1667 (1957).
(8) H. C. Brown and W. A. Murphey, *J. Am. Chem. Soc.*, **73**, 3308 (1951).
(9) H. C. Brown and X. R. Mihm, *J. Am. Chem. Soc.*, **77**, 1723 (1955).
(10) W. A. Pryor, *J. Am. Chem. Soc.*, **80**, 6481 (1958).

The reaction between 2,6-lutidine, sulfur, and *t*-octylamine proceeded smoothly at only one methyl group to give *N*-(*t*-octyl)-6-methylthiopicolinamide (V). An attempt to cause V to react with



V

sulfur and *t*-octylamine was unsuccessful. Unreacted *N*-(*t*-octyl)-6-methylthiopicolinamide (V) was recovered nearly quantitatively.

The usual resonance interpretation[8,9] of the reactivity of 2- and 4-methylpyridines, which implies some exocyclic double bond character at the 2- and 4-positions, provides the basis for a possible explanation of the lack of reactivity of the second methyl group. The electron withdrawal tendency of the thione group at the 2- position in III or V might be expected to confer some exocyclic double bond character at the 2- position of the ring, thus diminishing the possibility of any exocyclic double bond character at the remaining methyl group in the 4- or 6- position. Such a resonance stabilization effect would be expected for a radical mechanism as well as for an ionic mechanism.

Products from the reactions of 2,3-lutidine and 2-methyl-5-ethylpyridine with sulfur and *t*-carbinamines were identified only by elemental analyses. While these indicate only that one methyl group reacted, it is likely that in both these materials reaction occurred at the 2 methyl group in view of the well established preferential reactivity of alkyl groups in the 2- and 4- positions of the pyridine nucleus over those in the 3- and 5- positions. This supposition is strengthened by the results of Porter,[1] who found that 3-methylpyridine, sulfur, and aniline gave no thionicotinanilide.

Good yields of *N*-*t*-alkylthiopicolinamides were obtained only when both sulfur and the methyl pyridine were used in excess. Variations in yield of *N*-*t*-octylthiopicolinamide (I) with changes in the mole ratio of reactants are shown in Table I. An attempt to carry out the reaction using a 1:1:3 mole ratio of α-picoline : *t*-octylamine : sulfur and employing 4 moles of pyridine as solvent gave only 10% of *N*-*t*-octylthiopicolinamide (I).

TABLE I

N-*t*-OCTYLTHIOPICOLINAMIDE (I)

α-Picoline, Moles	*t*-Octylamine, Moles	Sulfur, Moles	Yield, %[a]
1	1	6	10
1	1	3	13
2	1	3	44
4	1	3	76
2	1	6	94

[a] Based on *t*-octylamine. Once-distilled product containing a few percent unreacted sulfur.

Table II summarizes the preparations of *N*-*t*-alkylthiopicolinamides from the various methyl pyridines, sulfur, and *t*-carbinamines. Some of the reactions were carried out before the most desirable mole ratios had been determined and therefore may not represent the optimum yields. All the products were distillable yellow liquids. Analytical data showed that the once-distilled products contained a few percent of unreacted sulfur. Treatment with a solution of sodium sulfide in aqueous methanol successfully removed the unreacted sulfur so that subsequent distillation gave materials with elemental analyses corresponding to the theoretical values.

The attempted quaternization of *N*-*t*-octylthiopicolinamide (I) with ethyl iodide was unsuccessful.

EXPERIMENTAL

N-t-Alkylthiopicolinamides. (See Table II.) A mixture of the methyl pyridine, *t*-alkylamine, and sulfur was stirred and refluxed in a three-neck flask equipped with condenser, stirrer, and thermometer while hydrogen sulfide was evolved through the condenser. The mixture was cooled, diluted with heptane, filtered free of excess sulfur, and distilled. A mixture of the distilled product (1.0 mole), water (1.5 l.), methanol (0.5 l.), and sodium sulfide nonahydrate (0.75 mole) was stirred at 80° for 1.5 hr., cooled, and extracted with heptane. The heptane extract was dried over anhydrous potassium carbonate and distilled.

N-t-Octylthioisonicotinamide (IV). A mixture of 96 g. (3.0 moles) of sulfur, 93 g. (1.0 mole) of γ-picoline, and 65 g. (0.5 mole) of *t*-octylamine was stirred and refluxed for 12 hr., cooled, filtered, and distilled to give 75 g. of material, b.p., 140–180°/1 mm. Hg, which solidified. The distillate was stirred for 1.5 hr. at 80° with a mixture of 60 g. (0.25 mole) of sodium sulfide nonahydrate, 119 g. of methanol, and 450 g. of water. The material which solidified when the mixture was cooled was filtered off and recrystallized from heptane. There was obtained 34 g. (27%) of *N*-*t*-octylthioisonicotinamide (IV), m.p. 117.5–118.5°C.

Anal. Calcd. for $C_{14}H_{22}N_2S$: C, 67.15; H, 8.86; N, 11.19; S, 12.80. Found: C, 67.19; H, 8.90; N, 11.13; S, 13.00.

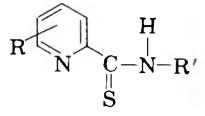
Hydrolysis and decarboxylation of N-(t-octyl)-4-methylthiopicolinamide (III). A mixture of 20 g. (0.076 mole) of *N*-(*t*-octyl)-4-methylthiopicolinamide (III), 100 g. of concentrated hydrochloric acid, and 200 g. of glacial acetic acid was stirred and refluxed for 3 hr., cooled, filtered, stripped to about 50 ml., made alkaline with excess 25% sodium hydroxide solution, and extracted with heptane. The aqueous portion was then made acidic with concentrated hydrochloric acid and stripped to near dryness. Successive extractions and evaporations were made using hot absolute ethyl alcohol to remove water and inorganic salts. The product was then taken up in isopropyl alcohol and precipitated with ether. Digestion of the precipitate with chloroform gave a solid which was dissolved in water and made to *p*H 6 with dilute aqueous sodium hydroxide. The solution was evaporated to dryness and the dried residue was extracted with warm acetone. The acetone extract was heated to distill off the acetone and then refluxed at about 200° for 5 min. in a large test tube. A picrate of the material remaining in the tube melted at 161–163° after recrystallization from ethyl alcohol. The melting point of a mixture with authentic γ-picoline picrate was 161–163°. The melting point of a mixture with authentic α-picoline was 130–140°.

Anal. Calcd. for $C_{12}H_{10}N_4O_7$: C, 44.73; H, 3.13; N, 17.39. Found: C, 44.89; H, 3.22; N, 17.24.

Attempted reaction of N-(t-octyl)-6-methylthiopicolinamide (V), *sulfur, and t-octylamine.* A mixture of 53 g. (0.20 mole) of *N*-(*t*-octyl)-6-methylthiopicolinamide (V), 19 g. (0.61

TABLE II

N-*t*-ALKYLTHIOPICOLINAMIDES



R	R′	Mole Ratio, Methyl Pyridine: Amine:S	Reflux Hr.	Final Pot Temp.	B.R./Mm. Hg	Yield,[a] %	Formula	Carbon, % Found	Carbon, % Calcd.	Hydrogen, % Found	Hydrogen, % Calcd.	Nitrogen, % Found	Nitrogen, % Calcd.	Sulfur, % Found	Sulfur, % Calcd.
H	*t*-C_8H_{17}	2:1:6	22	135	128–133/0.6	85	$C_{14}H_{22}N_2S$	66.86	67.15	8.76	8.86	11.16	11.19	12.82	12.80
H	*t*-$C_{11-14}H_{23-29}$[b]	2:1:6	20	143	160–175/0.7	87	$C_{17-20}H_{28-34}N_2S$	70.72	69.81–71.81	9.57	9.65–10.24	9.02	8.37–9.58	10.18	9.58–10.96
H	*t*-$C_{18-22}H_{37-45}$[c]	2:1:3	28	147	170–220/0.5	31	$C_{24-28}H_{42-50}N_2S$	74.05	73.78–75.27	10.80	10.84–11.28	7.05	6.27–7.17	7.82	7.18–8.21
6-CH	*t*-C_8H_{17}	2:1:6	8	164	136–151/0.6	90	$C_{15}H_{24}N_2S$	68.24	68.13	9.23	9.15	10.32	10.60	11.84	12.12
6-CH_3	*t*-$C_{11-14}H_{23-29}$	2:1:6	8	190	160–172/0.6	79	$C_{18-21}H_{30-36}N_2S$	71.06	70.53–72.35	9.81	9.87–10.41	8.57	8.04–9.14	10.13	9.20–10.46
4-CH_3	*t*-C_8H_{17}	2:1:6	4	190	150–160/1.0	82	$C_{15}H_{24}N_2S$	68.33	68.13	9.21	9.15	10.42	10.60	12.11	12.12
4-CH_3	*t*-$C_{11-14}H_{23-29}$	2:1:6	4	200	173–183/0.8	75	$C_{18-21}H_{30-36}N_2S$	71.27	70.53–72.35	9.87	9.87–10.41	8.62	8.04–9.14	9.96	9.20–10.46
5-CH_2 | CH_3	*t*-C_4H_9	4:1:3	10	162	120–123/0.4	22	$C_{12}H_{18}N_2S$	65.04	64.82	8.14	8.16	12.73	12.60	14.26	14.42
5-CH_2 | CH_3	*t*-C_8H_{17}	2:1:6	8	200	163–173/1.0	90	$C_{16}H_{26}N_2S$	69.06	69.02	9.27	9.41	10.02	10.06	11.61	11.51
5-CH_2 | CH_3	*t*-$C_{11-14}H_{23-29}$	1:1:3	6	218	175–190/0.6	50	$C_{19-22}H_{32-38}N_2S$	71.73	71.19–72.87	10.17	10.07–10.56	8.34	7.73–8.74	9.29	8.84–10.00
3-CH_3	*t*-$C_{11-14}H_{23-29}$	2:1:6	12	187	165–180/0.5	70	$C_{18-21}H_{30-36}N_2S$	71.33	70.53–72.35	9.95	9.87–10.41	8.62	8.04–9.14	9.79	9.20–10.46

[a] After purification by treatment with Na_2S. [b] Mixture of *t*-alkyl primary amines available as Primene 81-R from the Rohm and Haas Co. [c] Mixture of *t*-alkyl primary amines available as Primene JM-T from Rohm and Haas Co.

mole) of sulfur, and 13 g. (0.1 mole) of *t*-octylamine was stirred and heated at 150–175° for 2 hr. Another 13 g. (0.1 mole) of *t*-octylamine was added and the mixture was refluxed another 13 hr. The mixture was cooled, diluted with 200 ml. of heptane, and filtered. The residue was washed with heptane and dried to give 19 g. (0.61 mole) of unreacted sulfur. The combined filtrates were distilled to give 52 g. (98%) of unreacted *N*-(*t*-octyl)-6-methylthiopicolinamide (V), b.r. 135–140°/0.6 mm. Hg. There was 1 g. of residue.

Attempted quaternization of N-t-octylthiopicolinamide (I). A mixture of 25 g. (0.1 mole) of *N*-*t*-octylthiopicolinamide (I), 200 ml. of acetonitrile, and 20 g. (0.13 mole) of ethyl iodide was refluxed for 15 hr., cooled, and distilled free of ethyl iodide and acetonitrile. There remained a residue of 25 g. (0.1 mole) of unreacted *N*-*t*-octylthiopicolinamide (I).

Acknowledgment. I am indebted to Dr. C. L. Levesque and Dr. J. L. Rainey for helpful discussions, to Mrs. Alice Cannon for technical assistance, to Mr. L. A. Clement for the infrared data and interpretations, and to Mr. C. W. Nash and his associates for the elemental analyses.

BRISTOL, PA.

[CONTRIBUTION FROM THE DEPARTMENT OF MEDICINE, WESTERN RESERVE UNIVERSITY AND THE UNIVERSITY HOSPITALS]

Preparation of Pregnane-3α,16α,20α-triol and of Two of Its Stereoisomers[1]

H. HIRSCHMANN AND MARGARET A. DAUS

Received March 2, 1959

The preparation of pregnane-3α,16α,20α-triol, of pregnane-3α,16α,20β-triol, and of pregnane-3β,16α,20β-triol is described and some of the characteristics of the infrared spectra of 16α-acetoxy steroids are pointed out.

Three 16α-hydroxysteroids with the pregnane skeleton have been isolated from urine. Two of these, allopregnane-3β,16α,20β-triol[2,3] and its 20-epimer[4,5] are found during pregnancy, while Δ⁵-pregnene-3β,16α,20α-triol[5] was encountered in a case of an adrenal tumor. The last observation suggested the possibility that the adrenal cortex might effect hydroxylations at C-16. This hypothesis was verified by Rao and Heard[6] and by Neher *et al.*[7] The Swiss group isolated 3β,-16α-dihydroxyallopregnan-20-one from an adrenal extract while the Canadian workers obtained isotopically labeled 16α-hydroxyprogesterone upon the incubation of tagged progesterone with an adrenal homogenate. If the metabolism of 16α-hydroxyprogesterone in man follows the normal pattern its chief urinary excretion product is not one of the known triols but pregnane-3α,16α,20α-triol. To facilitate the search for this compound we have carried out its synthesis from a degradation product of sapogenins, 3β-acetoxy-Δ¹⁶-pregnen-20-one.[8]

Two routes were explored. The first gave only a very low yield of the desired product, but proceeded in a stepwise manner which allowed one to deduce the structure of the final product with assurance. The 16-hydroxyl group was introduced into Ia by the benzyl alcohol method[9] which in the case of 3β-hydroxy-Δ⁵,¹⁶-pregnadien-20-one[10] and of Ib[11] has yielded hydroxy steroids with the α configuration at C-16 and the normal orientation of the side chain. The rotations of the triacetates IVb, VIIIb, and IXb corroborate these assignments also for our conversion of Ia to III. The formate group at C-3 even in the axial orientation is sufficiently reactive to allow its selective hydrolysis as was required in the conversion of III to V. The product although formulated as a 3β-hydroxysteroid failed to precipitate with digitonin. However, the structure of V follows from the disappearance of the strong formate absorption at 8.45 μ and the retention of the acetate band at 8.06 μ. The free hydroxyl group of V was oxidized with chromic acid to the acetoxydiketone VI which was reduced selectively with sodium borohydride in isopropanol[12,13] and pyr-

(1) This investigation was supported by grant C-1679 of the National Institutes of Health, U. S. Public Health Service.

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(8) We are greatly indebted to Dr. J. J. Pfiffner of Parke, Davis and Company for a gift of this compound.

(9) H. Hirschmann, F. B. Hirschmann, and J. W. Corcoran, *J. Org. Chem.*, **20**, 572 (1955).

(10) H. Hirschmann, F. B. Hirschmann, and M. A. Daus, *J. Am. Chem. Soc.*, **74**, 539 (1952).

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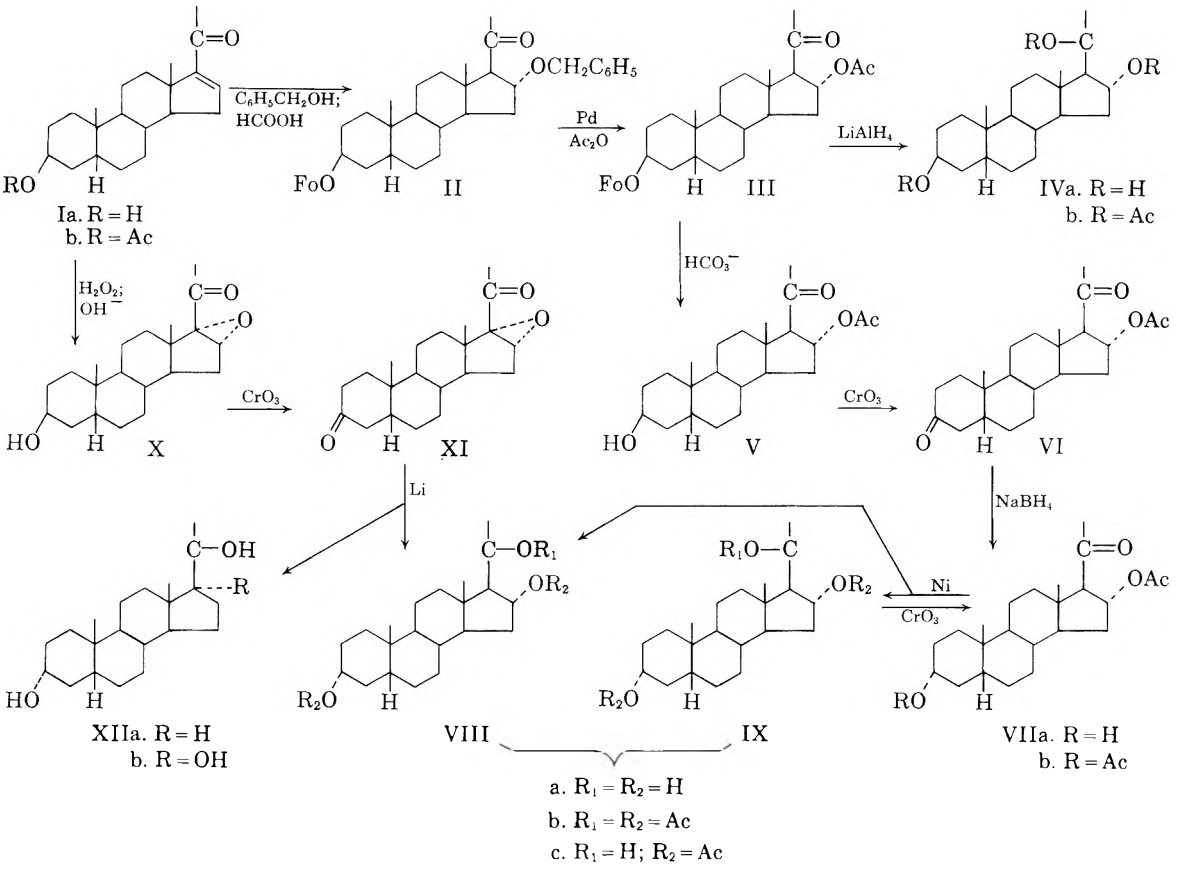
(13) The use of this solvent instead of methanol stabilized with alkali[14b] seems advantageous for the partial reduction of ketones (such as VI) which are sensitive to alkali.

idine[14] to a hydroxyacetoxyketone VIIa. The expected site for this reduction is the ketone group at C-3.[14] Evidence for the retention of the 20-keto-group was obtained by the exposure of VIIb to alkali which caused the appearance of a strong band at 239 mμ characteristic of an α-β unsaturated ketone. Compound VIIa, therefore, must have retained the 16-acetoxy-20-ketone grouping and consequently possesses its free hydroxyl group at C-3. The α configuration of this hydroxyl group is consistent with the principal course of reduction of other 5β 3-ketosteroids by sodium borohydride,[14] with the non identity of VIIa and V and with the shorter wave lengths[15,16] of the alkyl oxygen vibrations at C-3 of VIIa and b as compared to those of V and of 3β,16α-diacetoxypregnan-20-one[11] (9.78μ).



Reductions with lithium aluminum hydride of 20-ketones containing either a hydroxy[9] or ether[5,10] group at the 16α position had furnished both epimers of the 20-hydroxy steroids. However, when the 16α-acetoxy-20-ketone III was reduced by the same method only one triol IVa could be isolated which was assigned the 20β configuration on the basis of its rotation.[17] In view of this failure to obtain the α-isomer, compound VIIb was subjected to an alternative reduction method, hydrogenation with Raney nickel,[9] which gave a mixture of the two diacetates VIIIc and IXc in which the β-isomer predominated. Again configurations were determined by comparing rotations of the di- and triacetates with the values computed for the two epimeric series. The resulting assignments were confirmed by infrared spectroscopy. Only one isomer showed hydrogen bonding between the hydroxyl group and ester carbonyl. The required close approach of these groups is possible only[18] if the hydrogen rather than the methyl at C-20 is directed towards the angular methyl group.[5,19] In agreement with this expectation, the α-isomer was the one to show hydrogen bonding. An anomaly in R_F values probably can be explained on the same basis. In paper chromatographic separations of simple 20-epimeric alcohols the α-isomer if

(14) (a) O. Mancera, H. J. Ringold, C. Djerassi, G. Rosenkranz, and F. Sondheimer, *J. Am. Chem. Soc.*, **75**, 1286 (1953); (b) A. H. Soloway, A. S. Deutsch, and T. F. Gallagher, *J. Am. Chem. Soc.*, **75**, 2356 (1953), and references cited in these papers.

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(16) R. N. Jones and F. Herling, *J. Am. Chem. Soc.*, **78**, 1152 (1956).

(17) L. H. Sarett, *J. Am. Chem. Soc.*, **71**, 1175 (1949).

(18) It is assumed that the 16α-acetoxy group is in the usual coplanar conformation of an ester group (G. W. Wheland, *Resonance in Organic Chemistry*, J. Wiley and Sons, Inc., New York, 1955, p. 235). According to L. P. Kuhn [*J. Am. Chem. Soc.*, **74**, 2492 (1952)] hydrogen bonding to oxygen is possible only if the distance of these atoms is less than 3.3 Å.

(19) J. W. Corcoran and H. Hirschmann, *J. Am. Chem. Soc.*, **78**, 2325 (1956).

separated at all traveled slower[20] suggesting a somewhat greater solubility in the hydroxylic phase. In contrast the 20-α-isomer VIIIa traveled 3 times as fast as the 20β compound IXa. This behavior is understandable if internal hydrogen bonding of VIIIa would diminish its solvation with the hydroxylic solvent and thereby reduce its solubility in the stationary phase. In agreement with this view the spectrum of crystalline VIIIa but not of IXa showed a shoulder in the hydroxyl region indicative of intramolecular hydrogen bonding.

A far shorter route to pregnane-3α,16α,20α-triol was suggested by the work of Camerino and Alberti[21] who obtained Δ^5-pregnene-3β,16α,20α-triol by reduction of 3β-hydroxy-16α,17α-epoxy-Δ^5-pregnen-20-one with sodium and alcohol. Application of this method to 16α,17α-epoxypregnane-3,20-dione (XI)[22] gave a rather large amount of oily by-products, but this could be avoided when the reduction was carried out with lithium in ethylamine.[24] The desired pregnane-3α,16α,-20α-triol was the main product, but its purification was complicated by the presence of pregnane-3α,20α-diol (XIIa) and of pregnane-3α,17α,20α-triol (XIIb) which could not be removed by recrystallization. Other impurities probably included the 20β-isomers of VIIIa, XIIa, and XIIb. Oxidation with periodic acid in the presence of sulfuric acid[25] removed the 17,20-glycols and countercurrent distribution followed by recrystallization gave pregnane-3α,16α,20α-triol identical in every respect with the sample obtained by the stepwise synthesis.

When the spectroscopic measurements obtained in the present study were compared with earlier findings[3,5,9-11] certain regularities emerged which seem to possess diagnostic significance. All 16α-acetoxy-20-ketones that could be examined in carbon disulfide[26] in sufficient concentration and with sufficient resolution to permit reliable measurement of the ketone peak showed a maximum at 5.84 μ (7 examples), while 16α-benzyloxy-20-ketones possessed the normal peak for 20-ketones (5.86 μ). Shifts in this direction have been observed for many steroid ketones with an acetoxy group at the α carbon atom.[27] Those now reported for an ester group at the β carbon are rather small if the substituents are *trans* to each other but a larger displacement (to 5.82 μ) was noted with a 16β-acyloxy-20-ketone, the oxidation product of pseudotigogenin diacetate.

As far as we are aware, the steroidal 3-formates previously studied were all of the equatorial type (3β-formoxy-Δ^5 or 3α-formoxy-5β) and had an acyl-oxygen absorption wave length of 8.48 $\pm$ 0.01μ [9,28] or longer.[29a] Two 3β-formoxy-5β compounds (II and III) both absorbed at 8.45 μ[29b] and this band in spite of the axial orientation of the ester group had a simple contour. Evidently axial acetates[16] and formates differ in this respect.

The examination of five 3α,16α,20β-triacetoxy steroids revealed the presence of 4 bands in the finger print region which were of constant wave length within rather close limits ($\pm$ 0.02 μ). These were a strong band at 9.25 or 9.26 μ, two bands of medium intensity at 10.69 $\pm$ 0.01 and 10.80 $\pm$ 0.02, and a weak one at 9.00 or 9.01 μ (1081–1080, 936–935, 928–924, 1111–1110 cm.$^{-1}$). In addition, compounds with a 5α-hydrogen or a 5–6 double bond had common peaks at 8.85 to 8.88 μ, 9.54 $\pm$ 0.01 μ, and 10.53 μ (1130–1126, 1049–1047, 950 cm.$^{-1}$) while those of the 5β-series absorbed at 8.89 $\pm$ 1, 9.41, and 10.48 or 10.49 μ (1126–1124, 1063, 954–953 cm.$^{-1}$). The common finger print bands of three 3,16α,20α-triacetoxysteroids with either a double bond or an α or β hydrogen at C-5 were at 8.67 + 0.01, 10.50 $\pm$ 0.01 (both fairly intense) 8.89, 9.05 $\pm$ 0.02 and 10.62 $\pm$ 0.02 μ (1153–1152, 953–951, 1125, 1107–1103, 943–940 cm^{-1}). The number of characteristic frequencies is smaller than those listed[16] for simple 20α or β-acetoxy-5α-steroids without another substituent in the vicinity of C-20. As would be expected several of our bands differ from those described for the simpler structures, but a number of others including the important H and I bands appear to be but little affected by the introduction of the

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(21) B. Camerino and C. G. Alberti, *Gazz. chim. ital.*, **85**, 56 (1955).

(22) The method of P. L. Julian, C. C. Cochrane, A. Magnani, and W. J. Karpel [*J. Am. Chem. Soc.*, **78**, 3153 (1956)] which was used in the preparation of X has given in other cases almost exclusively[23] the 16α17α-epoxide. The rotation of X confirms this assignment. After the preparation of X and XI was completed, Kenney, Weaver, and Wall [*J. Am. Chem. Soc.*, **80**, 5568 (1958)] described the synthesis of these compounds from Ib. The melting points agree but the rotation of our X differs widely from that of their product (wrong sign ?). XI was obtained by a different route by Mancera *et al.*[14a]

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(24) (a) R. A. Benkeser, R. E. Robinson, D. M. Sauve, and O. H. Thomas, *J. Am. Chem. Soc.*, **76**, 631 (1954); (b) A. S. Hallsworth and H. B. Henbest, *J. Chem. Soc.*, 4604 (1957).

(25) R. I. Cox, *Biochem. J.*, **52**, 339 (1952).

(26) Except when noted otherwise all infrared measurements and comparison data refer to solutions in carbon disulfide.

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(28) R. N. Jones, P. Humphries, F. Herling, and K. Dobriner, *J. Am. Chem. Soc.*, **73**, 3215 (1951); E. S. Rothman and M. E. Wall, *J. Am. Chem. Soc.*, **81**, 411 (1959).

(29a) S. Archer, T. R. Lewis, C. M. Martini, and M. Jackman, *J. Am. Chem. Soc.*, **76**, 4915 (1954).

(29b) After submission of this paper we noted three examples of axial 3-formates with maxima at 8.44 and 8.45 μ. [F. C. Chang and R. T. Blickenstaff, *J. Am. Chem. Sec.*, **80**, 2906 (1958)].

16α-acetoxy group. Due to its greater variability the C-16-oxygen stretching vibration of 16α-acetates is probably not included in these listings. This peak is most likely identical with the strongest maximum in the 10 μ region in the spectra of 16α-acetoxyprogesterone[9] and 16α-acetoxypregnane-3,20-dione (9.62 and 9.67 μ, respectively). The presence of a 16-acetate band can be obscured in steroids containing a carbon-oxygen single bond at C-3 if its stretching vibration also falls into the 9.6 to 9.7 μ region. Accordingly,[16] only a single peak was seen in the spectra of 3β-acetoxy-Δ⁵ and 3β-hydroxy-5β compounds, but suggestive evidence for a second vibration was obtained from the curves of 3β-acetoxy-5α steroids in the displacement of the C-3 maximum from its normal range[16] to shorter wave lengths (9.68 to 9.70 μ). The remaining 14 spectra of 16α-acetates showed aside from the C-3 peak either another clearly resolved strong peak or at least a well defined shoulder on the C-3 stretching maximum. These observations comprised 20-hydroxysteroids of either configuration at C-20, their acetates, 20-ketones and a methyl etianate. There was no apparent correlation between band position (9.60–9.69 μ) and the nature of the side chain. In view of the constancy of the phenomenon, and the intensity of the absorption, which in several cases surpassed that of the C-3 peak, it seems probable that the band near 9.64 μ (1037 cm^{-1}) represents the C-16-oxygen stretching vibration of 16α-acetoxypregnanes.

EXPERIMENTAL[26,30]

Reports on infrared maxima are generally limited to those signifying functional groups such as hydroxyl (~2.78), 20-ketone (~5.86), acetate (~5.75 and 8.06) and formate (~5.80 and 8.45 μ) and to the carbon-oxygen bands in the 9.6 to 9.8 μ range. However, all maxima and inflections except very weak ones (strong ones underlined) are listed for the triacetates IVb, VIIIb, and IXb in the range 7.55 to 11.4 μ and for VIIIa from 7.4 to 12.5 μ.

3β-Formoxy-16α-benzyloxypregnan-20-one (II). The treatment of 500 mg. of 3β-hydroxy-Δ¹⁶-pregnen-20-one (Ia) with 15 ml. of a 3% solution of potassium hydroxide in benzyl alcohol was carried out for 3 hr. at 24° as described previously.[9,10] The crude reaction product was dissolved in 28 ml. of benzene and 14 ml. of 98–100% formic acid[9] and kept at 50–55° for 90 min. under anhydrous conditions while the pressure was reduced sufficiently to permit the distillation of 20 ml. of liquid. The reaction product (741 mg.) was fractionated on a column of 33 gm. of silica gel–Celite into the formate of (I) and into compound II by elution with mixtures of benzene and petroleum ether (1:2 to 2:1) and with benzene. The later eluates were recrystallized from acetone to give 313 mg. of 3β-formoxy-16α-benzyloxypregnan-20-one (II) melting at 153–158°. The analytical sample showed m.p. 157–159.5° and λ_{max} 5.80, 5.86, 8.45, 13.65, and 14.36 μ (last two benzyloxy[9–11]).

Anal. Calcd. for $C_{29}H_{40}O_4$: C, 76.95; H, 8.91. Found: C, 76.60; H, 8.94.

It should be noted that the more readily available 3β-acetoxy-Δ¹⁶-pregnen-20-one (Ib) could not be used in place of (Ia) as starting compound in the benzylation reaction since the alcoholysis of the acetate at C-3 was incomplete under the above conditions. We have obtained Ia from its acetate by heating 310 mg. of the latter in 122 ml. of dioxane and 48.8 ml. of 2.5% aqueous tetramethylammonium hydroxide under a reflux for 2 hr. and recrystallization of the reaction product from acetone–petroleum ether to give Ia with m.p. 183–185°.[32] After the completion of the hydrolysis experiment another procedure which minimizes addition reactions to the double bond was described.[33]

3β-Formoxy-16α-acetoxypregnan-20-one (III). A solution of 191 mg. of 3β-formoxy-16α-benzyloxypregnan-20-one (II) in 153 ml. of 95% ethanol was stirred magnetically for 2 hr. in the presence of hydrogen and of 154 mg. of pre-reduced and washed[9] palladium (5%) on charcoal. After the removal of catalyst and solvent the product was dissolved in 2 ml. of pyridine and acetylated with 1 ml. of acetic anhydride at 25° for 16 hr. The acetate was recrystallized from dilute methanol. The mother liquors were chromatographed on silica gel–Celite. The yield was 135 mg. 3β-Formoxy-16α-acetoxypregnan-20-one (III) melted at 102.5–105.5° and had $[\alpha]_D^{25}$ +37° (*c* 0.7) and λ_{max} 5.75, 5.81 (unresolved formate and ketone), 8.06, 8.45, 9.67 (C-16) μ.

Anal. Calcd. for $C_{24}H_{36}O_5$: C, 71.25; H, 8.97. Found: C, 71.11; H, 9.04.

3β-Hydroxy-16α-acetoxypregnan-20-one (V). A mixture of 152 mg. of 3β-formoxy-16α-acetoxypregnan-20-one (III) in 51 ml. of methanol and of 1.53 ml. of 1*N* aqueous potassium bicarbonate was swirled until the precipitate was dissolved, was kept at 23° for 6 hr. and then distributed between 600 ml. of ether and 300 ml. of water. The ether phase was washed neutral and gave 148 mg. of residue which was chromatographed on a column of 7.4 gm. of silica gel–Celite with benzene containing 10% ether as the eluant. The later eluates (91 mg.) were recrystallized from ligroin and gave 83 mg. of V, while the earlier fractions (47 mg.) were mostly starting material which on rehydrolysis furnished an additional 19 mg. of V. These two zones were separated by higher melting material from which a product with the infrared spectrum of 3β-hydroxy-Δ¹⁶-pregnen-20-one and the m.p. 179–181.5° was isolated. Another higher melting fraction (dihydroxyketone?) was obtained by elution with benzene containing 50% ether. In view of these side products the two-step hydrolysis procedure was preferred to a single longer hydrolysis period.

3β-Hydroxy-16α-acetoxypregnan-20-one showed a m.p. of 134–135.5° or a double m.p. (89° and 137°), $[\alpha]_D^{27}$ +43° (c = 0.7) and λ_{max} at 2.77, 5.74, 5.84, 8.06, and 9.70 μ. A solution of 0.2 mg. of compound V in 0.01 ml. of 80% ethanol when mixed with 1 or 2 volumes of 1% digitonin in the same solvent showed no precipitate.

Anal. Calcd. for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64. Found: C, 73.57; H, 9.65.

16α-Acetoxypregnane-3,20-dione (VI). A solution of 149 mg. of 3β-hydroxy-16α-acetoxypregnan-20-one (V) in 14.8 ml. of acetic acid was treated with an equimolar amount of

(30) All melting points reported are corrected. Rotations were measured in 95% ethanol except when noted otherwise. The extractions and washings of 16-oxygenated 20-ketones were done rapidly in a cold room with chilled solvents and solutions. The silica gel–Celite mixture used in absorption chromatography was 2:1 and was prewashed as described.[19] The ligroin had b.p. 90–96°, the petroleum ether 60–70°. Paper chromatograms were run in the solvent system toluene, isooctane, methanol, and water (15:5:16:4)[31] and examined after reaction with a 10% solution of phosphomolybdic acid in ethanol and heating to 96° for 1 min.

(31) C. de Courcy, *J. Endocrinol.*, **14**, 164 (1956).

(32) R. E. Marker and co-workers [*J. Am. Chem. Soc.*, **62**, 3350 (1940); **64**, 210, 468 (1942)] reported a variety of melting points (188–190°, 169–172°, 180–183°), Wall *et al.*[33] gave 186–188°.

(33) M. E. Wall, H. E. Kenney, and E. S. Rothman, *J. Am. Chem. Soc.*, **77**, 5665 (1955).

chromium trioxide in 2 ml. of 90% acetic acid at 25° for 3 hr. The excess oxidant was reduced with methanol and the mixture taken up in ether and then washed with water, dilute sodium carbonate, and water. The neutral product was recrystallized from ligroin to yield 135 mg. of compound VI melting at 167–169°. The analytical sample melted at 168.5–169.5° and occasionally on reheating at 164°. $[\alpha]_D^{26}$ +51° (*c* 0.6). The spectrum showed λ_{max} 5.74, 5.83 (unresolved), 8.06, 9.67 μ, but no hydroxyl absorption.

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 74.04; H, 9.33.

3α-Hydroxy-16α-acetoxypregnan-20-one (VIIa). A solution of 109.6 mg. of 16α-acetoxypregnane-3,20-dione (VI) (0.293 mM.) in 11.7 ml. of isopropanol (distilled after a 2-hour treatment with sodium borohydride) was mixed with 2.93 ml. of a 0.05*M* solution of sodium borohydride (purified according to Brown *et al.*[12] and assayed according to Lyttle *et al.*[34]) in pyridine and kept under nitrogen for 20 min. at 25°. The mixture was chilled, acidified, and distributed between hydrochloric acid and ether. The ether layer was washed with sodium bicarbonate and with water and yielded 108 mg. of an oil which was chromatographed on silica gel–Celite with benzene containing 10 to 20% ether. The later eluates were recrystallized from ligroin to yield VIIa melting at 108–110° with infrared peaks at 2.78, 5.75, 5.84, 8.06, 9.59 (shoulder, C-3), and 9.68 μ (C-16).

Anal. Calcd. for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64. Found: C, 73.46; H, 9.97.

For preparatory purposes it is advantageous to purify the reduction product after chromatography by acetylation and recrystallization. In this manner 255 mg. of VI gave 118 mg. of pure VIIb. Spectrographic examination of the earlier eluates (not acetylated) disclosed the presence of VI and of Δ^{16}-20-ketone.

3α,16α-Diacetoxypregnan-20-one (VIIb). Sixty-six mg. of 3α-hydroxy-16α-acetoxypregnan-20-one (VIIa) were acetylated with 1 ml. of pyridine and 0.5 ml. of acetic anhydride at 26° for 16 hr. The acetate was recrystallized 3 times from ligroin and gave 66 mg. of compound VIIb melting at 127–129° with λ_{max} 5.75, 5.84, 8.08, 9.61 (shoulder, C-16), and 9.73 μ (C-3). A solution of 0.16 mg. of VIIb in 1.5 ml. of 2% potassium hydroxide in *t*-butanol[33] was kept at 29° for 3.5 hr. The neutral reaction product in 10 ml. of 95% ethanol showed an absorption maximum at 239 mμ with an absorbance of 0.320 for a 1-cm. path length.

Reduction of 3α,16α-diacetoxypregnan-20-one (VIIb). A solution of 111 mg. of VIIb in 16 ml. of 95% ethanol and of 807 mg. of Raney nickel[35] were shaken with hydrogen for 9 hr. The catalyst was removed by centrifugation and the product (113 mg.) chromatographed on silica gel–Celite. The 20β isomer predominated in the earlier eluates (100 mg. with benzene containing up to 10% ether), the epimer in the later eluates (13 mg., with benzene containing 10 to 15% ether). To increase the proportion of the α isomer, the β-fractions were reoxidized with chromium trioxide in acetic acid for 2 hr. at 25° and the reaction product again reduced with nickel. The catalyst prepared according to Mozingo,[35] while less active than W-5,[36] gave a higher proportion of the α-isomer.

The main product *3α,16α-diacetoxypregnan-20β-ol* (IXc) was purified by recrystallization from petroleum ether. It showed m.p. 97–102°, $[\alpha]_D^{20}$ −43° (*c* 0.5) and λ_{max} 2.77, 5.76, 8.07, 9.60 (C-16), and 9.74 μ (C-3).

Anal. Calcd. for $C_{25}H_{40}O_5$: C, 71.39; H, 9.59. Calcd. for $C_{25}H_{40}O_5 \cdot 0.25(C_6H_{14})$: C, 71.99; H, 9.92. Found: C, 72.02; H, 9.83.

Compound IXc (18 mg.) was treated with 3 ml. of pyridine and 1.5 ml. of acetic anhydride at room temperature to yield 20 mg. of the amorphous *triacetate* (IXb) which showed $[\alpha]_D^{23}$ −19° (*c* 1.0) and λ_{max} ~8.08, 8.23, 8.37, 8.55, 8.90, 9.01, 9.26, 9.41, 9.61, 9.73, 9.87 (shoulder), 10.18, 10.30, 10.49, 10.69, 10.78, and ~11.28 μ. There was no hydroxyl peak. A mixture of 19 mg. of the triacetate, 60 mg. of sodium hydroxide, and 11 ml. of 80% ethanol were heated under a reflux for 100 min. The resulting *pregnane-3α,16α,20β-triol* (IXa) was recrystallized from acetone. Two modifications with m.p. 200–203° and 214–216° were observed. Paper chromatography showed a single spot with R_F = 0.08.

The fractions containing *3α,16α-diacetoxypregnan-20α-ol* (VIIIc) were purified by rechromatographing and recrystallizing from ligroin, dilute methanol, and from petroleum ether. The diacetate melted at 129–131° and had $[\alpha]_D^{22}$ −33° (*c* 0.3). The main hydroxyl peak was at 2.86 and a lesser one at 2.78 μ, the major acetate peak at 5.76, and the hydrogen bonded one at 5.82 μ. The ester peak at 8.07 had a shoulder at 7.96 μ. The alkyl oxygen stretching bands were at 9.74 (C-3) and 9.62 μ (shoulder, C-16). The compound was converted to the triacetate VIIIb and triol VIIIa by the procedures described for IXc. The *triacetate* again failed to crystallize. It showed $[\alpha]_D^{19}$ −27° (*c* 0.5) and λ_{max} ~8.06, 8.23, 8.39, 8.55, 8.67, 8.89, 8.94, 9.07, 9.18, 9.34, 9.65, 9.74, 9.83 (shoulder), 10.20, 10.51, 10.64 (shoulder), 10.76, 11.05, and 11.29 μ. *Pregnane-3α,16α,20α-triol* (VIIIa) was recrystallized from acetone and from dilute alcohol. It melted at 221–223° and showed in a KBr pressing λ_{max} 2.80 (shoulder), ~3.00, 7.48, 7.52 (shoulder), 7.75, 7.92, 8.03, 8.11, 8.24, 8.54, ~8.63, 8.96, 9.08, 9.18, 9.34, 9.56, 9.70, 9.81, 9.86 (shoulder), 10.01, 10.19, 10.46, 10.56, 10.71, 10.88, 11.11, 11.37, ~11.44 (shoulder), 11.72, and 11.96 μ. Paper chromatography revealed a single spot with R_F 0.26. The trichloroacetic acid fluorescence reaction[31] was negative.

Pregnane-3β,16α,20β-triol (IVa). A mixture of 79 mg. of 3β-formoxy-16α-acetoxypregnan-20-one (III), 210 mg. of lithium aluminum hydride, and 95 ml. of dry ether was made up at 0° and stirred at room temperature for 75 min. The crystalline product was acetylated and the resulting amorphous acetate chromatographed on alumina. Since the various eluates showed only minor differences in their infrared spectra they were combined, hydrolyzed, and recrystallized from mixtures of methanol and benzene to yield pregnane-3β,16α,20β-triol with m.p. 240–242° and rotation $[\alpha]_D$ −24° (*c* 0.6). On paper chromatography a single spot with extensive trailing was observed ($R_F \leq 0.10$).

Anal. Calcd. for $C_{21}H_{36}O_3$: C, 74.95; H, 10.78. Found: C, 75.01; H, 10.79.

Reacetylation gave triacetate IVb with $[\alpha]_D$ −39° (*c* 0.9) and λ_{max} ~8.09, 8.25 (shoulder), 8.40, 8.46 (shoulder), 8.66, 8.88, 9.01, 9.26, 9.41, 9.63, 9.77, 9.87 (shoulder), 10.13, 10.28, 10.40, 10.48, 10.70, 10.78, 10.99 and 11.20 μ.

3β-Hydroxy-16α,17α-epoxypregnan-20-one (X). A solution of 591 mg. of 3β-acetoxy-Δ^{16}-pregnen-20-one (Ib) in 45 ml. of methanol was cooled to 7° and mixed with 1.1 ml. of 4*N* aqueous sodium hydroxide and 2.2 ml. of 30% hydrogen peroxide. The mixture was kept at 22° for 18 hr. and distributed between ether and water. The ether phase was washed with water, ferrous sulfate, water, acetic acid, water, sodium carbonate, and water and gave 601 mg. of residue. This material, 1 g. of potassium hydroxide and 40 ml. of methanol were heated under a reflux for 2 hr. The neutral product (537 mg.), recrystallized from dilute acetone, gave 308 mg. of 3β-hydroxy-16α,17α-epoxypregnan-20-one with m.p. 225–229°. Chromatography of the mother liquors (alumina, benzene) and recrystallization furnished an additional 90 mg. The final product had m.p. 227–229°, $[\alpha]_D^{21}$ +62° (*c* 0.87, 95% ethanol[37]) and +57° (*c* 0.7, acetone) and λ_{max} 2.77 and 5.86 μ.

(34) D. A. Lyttle, E. H. Jensen, and W. A. Struck, *Anal. Chem.*, **24**, 1843 (1952).

(35) R. Mozingo, *Org. Syntheses*, **21**, 15 (1941).

(36) H. Adkins and H. R. Billica, *J. Am. Chem. Soc.*, **70**, 695 (1948).

(37) This solution proved to be supersaturated. Although no crystallization could be detected during the measurement, the rotation was repeated in acetone.

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.25; H, 9.36.

16α,17α-Epoxypregnane-3,20-dione (XI). A solution of 149 mg. of 3β-hydroxy-16α,17α-epoxypregnan-20-one (X) in 7.3 ml. of acetic acid was oxidized with chromium trioxide as described for (V) and the product recrystallized from ligroin to yield 122 mg. of XI which melted at 171–174°. λ_{max} ~5.84 μ (unresolved).

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 75.91; H, 9.19.

Reduction of 16α,17α-epoxypregnane-3,20-dione (XI). Ethylamine (25 ml.) was distilled from barium oxide into a two-neck flask containing 56 mg. of the epoxydione XI. The receiving vessel which was equipped with a soda lime tube and a magnetic stirrer was immersed in an ice salt bath. The still was removed, 190 mg. of lithium were added, and the vessel was stoppered. The mixture was stirred in a bath maintained at 0°. After 25 min. the blue color was discharged periodically by the addition of dry ethanol (4 portions of 0.5 ml.). When all of the lithium had been dissolved and ionized, the solvent was evaporated in a current of nitrogen at room temperature. The residue was distributed between ether and hydrochloric acid. The organic phase was washed free of acid and gave 58 mg. of crystalline residue. Partition chromatography on silica gel (solvent system ethyl acetate, iso-octane, methanol, and water 150:300:135:315) followed by recrystallization gave products which had satisfactory m.p. but contained impurities with R_F 0.33 and 0.64. The reaction product was subjected to a 50 transfer countercurrent distribution between phases prepared from iso-octane, toluene, methanol, and water 125:375:360:140. Impurities with R_F 0.07 (IXa?) and 0.12 were found only in the first 2 tubes. The contents of tubes 15–21 (which contained mainly the product with R_F 0.64 (XIIa) and a little of one with R_F 0.70) were recrystallized, acetylated, and recrystallized to give pregnanediol diacetate identified by its double m.p. 180–181°, 166.5°), mixture m.p. and infrared spectrum. VIIa was found in tubes 1–10 but only the first 3 were free of an impurity identified as pregnane-3α,17α,20α-triol by its R_F (0.33), by its fluorescence reaction with trichloroacetic acid[31] and by the conversion to a 17-ketosteroid by means of periodic acid. To free VIIIa completely from XIIb and its 20-epimer (R_F 0.41), 9.8 mg. of such a mixture in 1 ml. of acetic acid were treated with 1 ml. of a 0.2*M* solution of periodic acid in 1*N* aqueous sulfuric acid for 2.5 hr. at 26°. The neutral reaction product was recrystallized from acetone. Pregnane-3α,16α,20α-triol prepared from XI melted at 223.5–224° and agreed with the sample obtained from VII in the mobility on paper, and in the infrared spectra of the triacetate and of the free triol. There was no depression of m.p. on admixture. The yield was 14 mg.

Anal. Calcd. for $C_{21}H_{36}O_3$: C, 74.95; H, 10.78. Found: C, 75.36; H, 10.47.

Reference data for rotations. Approximate values for the molecular rotations in ethanol were computed from the set of standard values given by Barton and Klyne[38] and from the molecular rotations of allopregnane-3β,16α,20β-triol[39] −54°, of its triacetate[3] −208°, of allopregnane-3β,16α,20α-triol triacetate[5] −268° (all 3 in alcohol), of allopregnane-3β,20β-diol +12° (average)[40] and of its diacetate[41] +89° (both in chloroform). The calculated figures are compared with the experimental values which are given in parentheses: Compound IVa −50° (−82°), IVb −153° (−181°) as compared to pregnane-3β,16α,20α-triol +8°, triacetate −213°, compound VIIIc −112° (−140°), IXc −170° (−180°). $\Delta[M]_D^{VIIIb-VIIIc}$ +17°, $\Delta[M]_D^{IXb-IXc}$ +91° as compared to $\Delta[M]_D^{OAc-OH}$ for the acetylation of the 20-hydroxyl group of pregnane-3α,20ξ-diol, 20α −10° and 20β +105°.[17]

The molecular rotation differences between 3β-acetoxy-Δ⁵-pregnen-20-one[42] and its 16α,17α and 16β,17β epoxide[23] are −87° and −452° (in chloroform), respectively, while the one between 3β-hydroxypregnan-20-one[43] and X equaled −115° in ethanol.

Acknowledgment. The authors thank Dr. Irving Rothchild for the use of a Craig countercurrent distribution apparatus; Dr. Constance de Courcy for her advice about paper and partition chromatography and countercurrent distribution; and Dr. E. W. D. Huffman for the microanalyses reported in this paper.

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Notes

A department for short papers of immediate interest.

Preparation of O-(Isopropylmethylphosphono)-4-formyl-1-methylpyridinium Iodide Oxime

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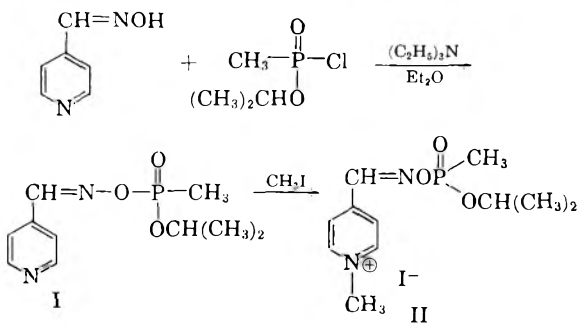
Received December 1, 1958

During initial screening studies of the velocity of reaction between isopropyl methylphosphonofluoridate (GB)[1] and a variety of oximes,[2] it was observed that many of the oximes reacted in two distinct acid-producing steps. The steps consisted of an initial phosphonylation of the oxime followed by breakdown of the phosphonylated oxime to secondary products.

With the discovery of the usefulness of pyridinium oximes such as 2-formyl-1-methylpyridinium iodide oxime[3] and 1,1′-trimethylenebis(4-formylpyridinium bromide) dioxime[4] in the treatment of poisoning by the organophosphorus anticholinesterases, a detailed investigation of the reaction between oximes of this general class and GB was undertaken.[5] As a part of this study, it was desirable to obtain a sample of a typical phosphonylated pyridinium oxime, *i.e.*, *O*-(isopropyl methylphosphono)-1-methyl-4-formylpyridinium iodide oxime.

We have prepared this compound by the reaction of pyridine-4-aldoxime with isopropyl methylphosphonochloridate in nonaqueous solution[6] followed by quaternization with methyl iodide according to the following scheme.



Compound II is a powerful inhibitor of eel acetylcholinesterase with a rate constant at *p*H 7.4 and 25° = 4.7–5.7 × $10^7 M^{-1}$ min.$^{-1}$. Its LD^{50} in white mice *via* the intravenous route of administration is 0.2 mg./kg. Detailed studies of the hydrolysis of this compound are in progress and will be reported later.

EXPERIMENTAL

Preparation of O-(isopropylmethylphosphono)pyridine-4-aldoxime (I). Isopropyl methylphosphonochloridate, 17.2 g. (0.11 mole), was added dropwise with stirring to a cooled solution of 12.2 (0.1 mole) of pyridine-4-aldoxime and 11.1 g. (0.11 mole) of triethylamine in 500 ml. of absolute diethyl ether (the triethylamine was distilled over KOH and the ether was dried over sodium). The temperature of the solution was maintained below 25° during the addition. After standing overnight the triethylamine hydrochloride which had precipitated was filtered from the solution and the ether was removed under vacuum, at bath temperature below 0°, leaving a light yellow viscous oil. The oil was heated to 50° (bath temperature) under high vacuum to remove the last traces of solvent. (An attempt to distill this oil at 0.2 mm. resulted in decomposition; a volatile fraction which distilled and solidified in the receiver, was found to be 4-cyanopyridine m.p. 80°C. The residue was a viscous, strongly acidic liquid believed to be isopropylmethylphosphonic acid.) A total of 23 g. (97%) of the desired product was obtained. This product was used, without further purification in the subsequent synthesis.

Anal. Calcd. for $C_{10}H_{15}N_2PO_3$ C, 49.59; H, 6.19; N, 11.57; P, 12.81. Found: C, 48.9; H, 6.4; N, 11.3; P, 12.0.

Preparation of O-(Isopropylmethylphosphono)-4-formyl-1-methylpyridinium iodide oxime (II). An excess of methyl iodide (0.04 mole) was added to an ether solution containing 4.8 g. (0.02 mole) of I. The mixture was allowed to stand at room temperature overnight after which an orange-red oil separated from the solution. This oil was triturated with several 50 ml. portions of anhydrous diethyl ether; it solidified while drying over P_2O_5 in vacuo at room temperature. The yield of II was 7.0 g. (91%) m.p. 97° dec. The material is an extremely hydroscopic orange powder. It decomposes slowly upon standing at room temperature, even in a closed vessel, but can be stored at 0°, in a desiccator over P_2O_5 for several months with little or no decomposition. All attempts to recrystallize this material resulted in lowered antiacetylcholinesterase activity. On the basis of the phosphorus analysis the sample is 91% pure.

Anal. Calcd. for $C_{11}H_{18}N_2PI$: C, 34.4; H, 4.7; N, 7.3; P, 8.1; I, 33.1. Found: C, 34.0; H, 4.6; N, 7.1; P, 7.4; I, 34.4.

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(1) GB is the code designation given this compound by the U. S. Army Chemical Corps.

(2) B. E. Hackley, Jr., Ph.D. Dissertation. University of Delaware, 1956. University Microfilms, Ann Arbor, Mich., 1958.

(3) For historical references see I. B. Wilson, *Biochimica et Biophysica Acta*, **27**, 196 (1958).

(4) E. J. Poziomek, B. E. Hackley, Jr., and G. M. Steinberg, *J. Org. Chem.*, **23**, 714 (1958).

(5) To be reported elsewhere.

(6) J. H. Turnbull, *Chem. and Ind.* (*London*), 350 (1956).

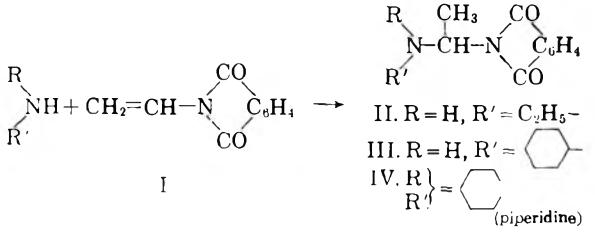
Reactions of *N*-Vinylimides with Amines

KIYOSHI YANAGI

Received November 18, 1958

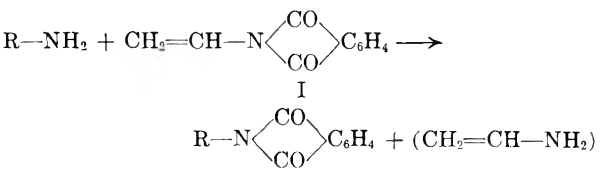
The reactions of *N*-vinylimides with inorganic compounds, such as halogen, hydrogen halide, and hydrogen are well known, but nothing is known about the reaction of *N*-vinylphthalimide, *N*-vinylsuccinimide and *N*-vinylsulfobenzimide with organic compounds. I have studied the reactions of *N*-vinylimides, described above, with amines, and addition reactions and imido interchange reactions were found.

Amines whose dissociation constants are larger than 10^{-4}, such as ethylamine[1] ($K=5.6\times10^{-4}$), cyclohexylamine[2] ($K=1.58\times10^{-4}$), piperidine[1] ($K=1.6\times10^{-3}$) were allowed to react with *N*-vinylphthalimide (I) to yield the adducts, *N*-(1-ethylaminoethyl)phthalimide (II), *N*-(1-cyclohexylaminoethyl)phthalimide (III) and *N*-(1-piperidinoethyl)phthalimide (IV).



The position of the addition is presumed to be α in the vinyl group, because, for example, the melting point of *N*-(2-piperidinoethyl)phthalimide[3] is 91° but the melting point of the present adduct is 126–127°. The results are shown in Table I.

Amines whose dissociation constants are smaller than 10^{-5}, namely, aniline[1] ($K = 3.83\times10^{-10}$), *p*-anisidine[4] ($K = 1.47 \times 10^{-9}$), *p*-aminobenzoic acid[5] ($K = 3.6 \times 10^{-12}$) and ethanolamine[1] ($K = 2.77 \times 10^{-5}$) were allowed to react with *N*-vinylphthalimide to cause imido interchange reactions and yield *N*-phenylphthalimide (V), *N*-4-methoxyphenylphthalimide (VI), *N*-4-carboxyphenylphthalimide (VII), and *N*-2-hydroxyethylphthalimide (VIII). The reactions were accelerated by organic acids.



V. C_6H_5—
VI. *p*-CH_3O—C_6H_4—
VII. *p*-HOOC—C_6H_4—
VIII. HO—CH_2—CH_2—

The effect of some organic acids in the reaction of *N*-vinylphthalimide with aniline are summarized in Table II. The yields were poor in the absence of organic acid but better in the presence of it.

TABLE II

THE EFFECTS OF ORGANIC ACIDS IN THE REACTION OF *N*-VINYLPHTHALIMIDE WITH ANILINE

Organic Acid	Dissociation Constant (25°)	Yield, %
		3
Acetic acid	1.753×10^{-5}	85
Benzoic acid	6.30×10^{-5}	64
Phenol	1.3×10^{-10}	17
p-Toluene Sulfonic acid		19

TABLE I

THE ADDUCTS OF *N*-VINYLIMIDES WITH AMINES

Adduct	M.P.	Yield, %	Formula	Analysis (%) Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
II[a]	146–147	84	$C_{12}H_{14}N_2O_2$	66.03	66.22	6.47	6.28	12.84	12.84
III[b]	183–184	95	$C_{16}H_{20}N_2O_2$	70.56	70.25	7.40	7.27	10.29	9.98
IV[c]	126–127	96	$C_{15}H_{18}N_2O_2$	69.79	69.88	7.02	7.22	10.85	10.94
X[c]	187–188	70	$C_8H_{14}N_2O_2$	56.45	56.43	8.29	8.29	16.46	16.42
XI[d]	138.5–139.5	94	$C_8H_{14}N_2O_3$	51.60	51.71	7.58	7.78	15.04	15.06
XII[c]	202.5–203.5	90	$C_{12}H_{20}N_2O_2$	64.25	64.25	8.99	9.04	12.49	12.37
XIII[e]	88.5–89.5	93	$C_{11}H_{18}N_2O_2$	62.83	62.72	8.63	8.69	13.32	13.39

[a] Recrystallized from benzene. [b] Recrystallized from ethanol–water or ethanol–ethyl acetate. [c] Recrystallized from ethanol. [d] Recrystallized from ethanol–benzene. [e] Recrystallized from ethyl acetate–petroleum ether.

N-vinylsuccinimide (IX) was allowed to react with ethylamine, ethanolamine, cyclohexylamine, and piperidine to yield *N*-(1-ethylaminoethyl)succinimide (X), *N*-(1,2-hydroxyethylaminoethyl)-

(1) N. A. Lange, *Handbook of Chemistry*, 8th edition, Handbook Publishers, Inc., Sandusky, Ohio, 1952, p. 1229.

(2) A. Waksmundzki, *Roczniki Chem.*, **18**, 865 (1938); *Chem. Abstr.*, **33**, 6689 (1939).

(3) W. O. Kermack and J. F. Smith, *J. Chem. Soc.*, 3098 (1931).

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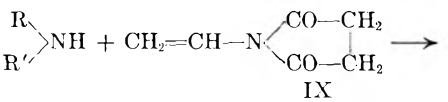
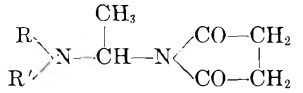
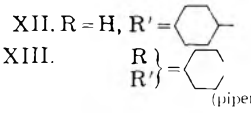
succinimide (XI), *N*-(1-cyclohexylaminoethyl)succinimide (XII) and *N*-(1-piperidinoethyl)succinimide (XIII) by the addition reaction. The results are shown in Table I.



IX



X. R = H, R′ = C_2H_5—
XI. R = H, R′ = OH—$(CH_2)_2$—



XII. R = H, R′ =
XIII. R, R′ = (piperidine)

N-vinylsulfobenzimide (XIV) was allowed to react with cyclohexylamine and aniline to yield products with empirical formula which correspond to *N*-cyclohexyl-*o*-sulfamoylbenzamide (XV) and *o*-sulfamoylbenzanilide (XVI), respectively. That is to say, neither addition reaction nor imido interchange reaction occurs in the case of *N*-vinylsulfobenzimide.

EXPERIMENTAL

Materials. *N*-vinylphthalimide,[6] *N*-vinylsuccinimide,[7] and *N*-vinylsulfobenzimide[8] were prepared by the pyrolysis of *N*-2-acetoxyethylphthalimide, *N*-2-acetoxyethylsuccinimide, and *N*-2-acetoxyethylsulfobenzimide, respectively.

Addition reactions of N-vinylphthalimide. A mixture of 5 g. of V.P.I. (*N*-vinylphthalimide) and 10 g. of ethylamine (33% water solution), a mixture of 5 g. of V.P.I. and 5.72 g. of cyclohexylamine, and a mixture of 4 g. of V.P.I. and 2.2 g. of piperidine in 15 ml. of benzene, were individually kept at room temperature for 3 hr. The precipitate was filtered and recrystallized. The results are summarized in Table I.

Imido interchange reactions of N-vinylphthalimide. A mixture of 5 g. of V.P.I., 3 g. of aniline, and 1 g. of acetic acid; a mixture of 5 g. of V.P.I., 3.56 g. of *p*-anisidine, and 1 g. of acetic acid; a mixture of 6 g. of V.P.I., 4.8 g. of *p*-aminobenzoic acid, and 1 g. of acetic acid; and a mixture of 4 g. of V.P.I., 1.6 g. of ethanolamine and 1 g. of acetic acid were individually heated at 100° for 4.5, 4, 5, and 10 hr., respectively. The resinous reaction products were rinsed with methanol and recrystallized from benzene and then *N*-phenylphthalimide, *N*-(4-methoxyphenyl)phthalimide, *N*-(4-carboxyphenyl)phthalimide, and *N*-(2-hydroxyethyl)-phthalimide were obtained.

N-phenylphthalimide: yield 85%, m.p. 209–210°.

Anal. Calcd. for $C_{14}H_9NO_2$: C, 75.32; H, 4.06; N, 6.28. Found: C, 75.61; H, 4.06; N, 6.54.

N-(4-methoxyphenyl)-phthalimide: yield 71%, m.p. 160–161°.

Anal. Calcd. for $C_{15}H_{11}NO_3$: C, 71.14; H, 4.37; N, 5.53. Found: C, 71.39; H, 4.55; N, 5.59.

N-(4-carboxyphenyl)-phthalimide: yield 80%, m.p. 261–262° (uncorr.).

Anal. Calcd. for $C_{15}H_9NO_4$: C, 67.41; H, 3.39; N, 5.24. Found: C, 67.18; H, 3.72; N, 5.13.

N-(2-hydroxyethyl)phthalimide: yield 70%, m.p. 128–129°.

Anal. Calcd. for $C_{10}H_9NO_3$: C, 62.82; H, 4.75; N, 7.33. Found: C, 63.06; H, 4.91; N, 7.12.

Addition reactions of N-vinylsuccinimide. A mixture of 6 g. of V.S.I. (*N*-vinylsuccinimide) and 12 g. of ethylamine (33% water solution), a mixture of 4 g. of V.S.I. and 2.2 g. of ethanolamine in 15 ml. of benzene, a mixture of 4 g. of V.S.I. and 7.5 g. of cyclohexylamine, and a mixture of 4 g. of V.S.I. and 3 g. of piperidine were individually kept at room temperature for 2, 0.5, 18 and 18 hr., respectively. The precipitates were filtered and recrystallized. The results are summarized in Table I.

N-cyclohexyl-o-sulfamoylbenzamide. A mixture of 4.5 g. of *N*-vinylsulfobenzimide and 6 g. of cyclohexylamine was stirred at room temperature. After 17 hr., the precipitate was rinsed with benzene to remove the resinous matter from it. Recrystallization from benzene gave *N*-cyclohexyl-*o*-sulfamoylbenzamide, yield 60%, m.p. 201–202.5°.

Anal. Calcd. for $C_{13}H_{18}N_2O_3S$: C, 55.31; H, 6.53; N, 9.93. Found: C, 55.23; H, 6.51; N, 9.81.

o-Sulfamoylbenzanilide. A mixture of 5.2 g. of *N*-vinylsulfobenzimide, 6 g. of aniline, and 2 ml. of acetic acid was heated at 100° for 3 hr. The reaction product was rinsed with benzene to remove the resinous matter. Recrystallization from ethanol gave 4.92 g. of *o*-sulfamoylbenzanilide, m.p. 189–190°.

Anal. Calcd. for $C_{13}H_9N_2O_3S$: C, 56.52; H, 4.83; N, 10.14. Found: C, 56.38; H, 4.51; N, 10.17.

Acknowledgment. The author is grateful to Prof. S. Akiyoshi of this Department, for his valuable suggestions and criticisms throughout the course of this work.

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(6) W. E. Hanford and H. B. Stevenson, U. S. Patent 2,276,840; *Chem. Abstr.*, **36**, 4637 (1942).

(7) W. E. Hanford and H. B. Stevenson, U. S. Patent 2,231,905; *Chem. Abstr.*, **35**, 3267 (1941).

(8) This is a new compound, m.p. 131–132° (from ethanol). *Anal.* Calcd. for $C_9H_7NO_3S$: C, 51.67; H, 3.37; N, 6.70. Found: C, 51.61; H, 3.36; N, 6.64.

Hydroxyethylation of Imides

Kiyoshi Yanagi and Saburo Akiyoshi

Received November 18, 1958

Several methods of preparing *N*-2-hydroxyethylimides are known.[1–3] The present paper describes a new method of hydroxyethylation of imides by ethylene carbonate, which is used not only as solvent but also as reagent.[4–7]

Though monocarboxylic amides showed no reaction, dicarboxylic imides and saccharin were easily hydroxyethylated in good yield by heating the mixture of imide and ethylene carbonate. Aromatic dicarboxylic imides reacted easily with-

(1) S. Gabriel, *Ber.*, **21**, 571 (1888).

(2) H. Dersin, *Ber.*, **54**, 3157 (1921).

(3) J. H. Billman and E. E. Parker, *J. Am. Chem. Soc.*, **65**, 761, (1943).

(4) M. S. Morgan and L. H. Cretcher, *J. Am. Chem. Soc.*, **68**, 781, (1946).

(5) W. W. Carlson and L. H. Cretcher, *J. Am. Chem. Soc.*, **69**, 1952, (1947).

(6) W. W. Carlson, U. S. Patent, 2,448,767; *Chem. Abstr.*, **43**, 673, (1949).

(7) R. Delaby, A. Sekera, and P. Chabrier, *Bull. soc. chim.*, **1951**, 392.

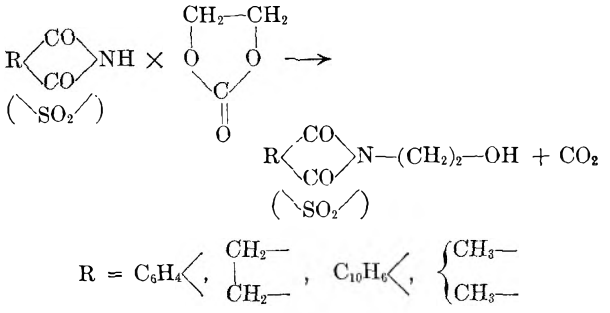
TABLE I

HYDROXYETHYLATION OF IMIDES

Imide	E.C.[a] (mol.) / Imide (mol.)	Alkali	Temp.	Time, Hr.	Yield, %
Phthalimide[b]	1.1	...	200	1.0	95
K-phthalimide[c]	2–3	...	140–160	0.5	60
Naphthalimide[d]	2.0	...	210	1.0	96
Succinimide[e]	1.0	Na_2CO_3 (0.5%)	190	1.0	86
Diacetamide[f]	1.0	Na_2CO_3 (0.5%)	195	1.0	70
Saccharin[g]	1.0	NaOH (0.5%)	210–220	1.0	93

[a] "E.C." represents ethylene carbonate. Product of American Cyanamid Co. [b] *Org. Syntheses*, **Coll. Vol. I**, 457 (1948). [c] *Org. Syntheses*, **Coll. Vol. I**, 119 (1948). [d] T. Maki and H. Hashimoto, *J. Chem. Soc. Japan, (Ind. Chem. Sec.)*, **54**, 480 (1951). [e] *Org. Syntheses*, **Coll. Vol. II**, 562 (1943). [f] L. Vanino, *Handbuch der Preparativen Chemie (2 Auflage)*, Ferdinand Enke, Stuttgart, II Bd., p. 207. [g] This was precipitated from the aqueous solution of its sodium salt by dilute hydrochloric acid, m.p. 225–227°.

out alkali carbonate or hydroxide. Aliphatic dicarboxylic imides reacted in the presence of alkali carbonate. Saccharin reacted only in the presence with alkali hydroxide. While potassium phthalimide was hydroxyethylated, sodium saccharin was not. The results are summarized in Table I.



The dissociation constants of phthalimide,[8] succinimide,[9] and saccharin,[10] which were hydroxyethylated in good yield, are 1.09×10^{-7}, 3.0×10^{-11} and 2.5×10^{-2} respectively (25°) and those of acetamide,[11] benzamide,[12] and acetanilide[13] which were not hydroxyethylated are 8.3×10^{-15}, *ca.* 1×10^{-14} and *ca.* 1×10^{-13}, respectively. Imides whose dissociation constants are larger than 10^{-11} – 10^{-12}, seem to be hydroxyethylated by ethylene carbonate.

EXPERIMENTAL

The mixture of imide and ethylene carbonate was heated under the conditions shown in Table I. The reaction products were treated as follows:

The reaction product of phthalimide and ethylene carbonate was recrystallized from water, m.p. 127°. The mixed melting point of this with *N*-2-hydroxyethylphthalimide was 126–127°. The infrared spectra of the two coincided.

The reaction product of potassium phthalimide with ethylene carbonate was washed with water and the precipitate was filtered. After it was treated with dilute hydrochloric acid, recrystallization from water gave N-2-hydroxyethylphthalimide. The mixed melting point of this with the authentic sample was 126–127°, and the infrared spectra of the two coincided.

The reaction product of naphthalimide and ethylene carbonate was recrystallized from water and N-2-hydroxyethylnaphthalimide was obtained, m.p. 172–173°.

Anal. Calcd. for $C_{14}H_{11}NO_3$: N, 5.80. Found: N, 5.99.

Distillation of the reaction product of succinimide with ethylene carbonate under vacuum gave N-2-hydroxyethylsuccinimide, b.p. 161–162° (3 mm. Hg), m.p. 62.5–63.5° (from acetone–carbon tetrachloride).

Anal. Calcd. for $C_6H_9NO_3$: C, 50.34; H, 6.34 N, 9.79. Found: C, 49.73; H, 6.53; N, 10.05.

Distillation of the reaction product of diacetamide with ethylene carbonate gave *N*-2-hydroxyethyldiacetamide, b.p. 129° (2.5 mm. Hg), 124° (1.5 mm.).

Anal. Calcd. for $C_6H_{11}NO_3$: N, 9.65. Found: N, 9.69.

The reaction product of saccharin with ethylene carbonate was recrystallized from water, and *N*-2-hydroxyethylsulfobenzimide was obtained, m.p. 105.5–106.5°.

Anal. Calcd. for $C_9H_9NO_4S$: C, 47.58; H, 3.99; N, 6.17. Found: C, 47.66; H, 3.54; N, 6.21.

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(8) J. K. Wood, *J. Chem. Soc.*, **89**, 1831 (1906).
(9) J. K. Wood, *J. Chem. Soc.*, **89**, 1837 (1906).
(10) N. A. Lange, *Handbook of Chemistry*, 8th ed., Handbook Publishers, Inc., Sandusky, Ohio (1952), p. 1229.
(11) G. E. Branch and J. O. Clayton, *J. Am. Chem. Soc.*, **50**, 1685 (1928).
(12) G. E. Branch and J. O. Clayton, *J. Am. Chem. Soc.*, **50**, 1686 (1928).
(13) C. G. Derick and J. H. Bormann, *J. Am. Chem. Soc.*, **35**, 1284 (1913).

Preparation of Halo-5-nitro-2-furanacrylanilides

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Received November 20, 1958

Several halo-5-nitro-2-furanacrylanilides have been reported as being effective anthelmintics and bacteriostats.[1–3] These compounds had been prepared by the reaction of purified 5-nitro-2-furanacryloyl chloride with a halogenated aniline under

(1) K. Miura, M. Ikeda, and S. Yasuda, *J. Pharm. Soc. Japan*, **75**, 57 (1955).
(2) M. Ikeda, *J. Pharm. Soc. Japan*, **75**, 628 (1955).
(3) M. Ikeyoshi and T. Miura, Jap. Patent **3871** (1957).

TABLE I

HALO-5-NITRO-2-FURANACRYLANILIDES

Compound	M.P.,[a] °C.	Formula	Analysis: Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Yield,[b] %
2′-Chloro-5-nitro-2-furanacrylanilide	187(lit.[8] 188)	$C_{13}H_9ClN_2O_4$	53.34	53.58	3.09	3.03	72
3′-Chloro-5-nitro-2-furanacrylanilide	205.5–206(lit.[8] 201)	$C_{13}H_9ClN_2O_4$	53.34	53.75	3.09	3.05	89
4′-Chloro-5-nitro-2-furanacrylanilide	216(lit.[8] 214)	$C_{13}H_9ClN_2O_4$	53.34	53.56	3.09	3.14	76.5
2′,4′-Dichloro-5-nitro-2-furanacrylanilide	217.5–218	$C_{13}H_8Cl_2N_2O_4$	47.71	48.05	2.46	2.49	
4′-Bromo-5-nitro-2-furanacrylanilide	230.5–231(lit.[8] 222)	$C_{13}H_9BrN_2O_4$	46.31	47.56	2.69	2.34	77.1

[a] Of material crystallized once from ethanol; the melting point was determined on a Fisher metal block melting point apparatus calibrated against standards. [b] Of uncrystallized material, which in each case melted over less than a 3° range (based on the amount of 5-nitro-2-furanacrylic acid used).

anhydrous conditions, in the presence of large amounts of copper shot.[3]

In the present work, the preparation of these compounds has been further studied and two procedures which are more convenient and more economical than the above method have been developed.

Attempts induce ethyl 5-nitro-2-furanacrylate to react with *p*-chloroaniline under a variety of conditions failed to produce the desired anilide. In a second method, 5-nitro-2-furanacrylic acid, *p*-chloroaniline, and phosphorus trichloride reacted in benzene to give a 65% yield of 4′-chloro-5-nitro-2-furanacrylanilide.

In a third procedure studied, a Schotten-Baumann procedure was found to be a very successful route to the anilides under study. It was found that the acid chloride preparation mixture could be treated directly with halogenated anilines, in the presence of aqueous base, to give a good yield of pure anilide which could be filtered directly from the reaction mixture.

5-Nitro-2-furanacrylic acid has been previously prepared by a Perkin condensation of 5-nitrofurfural and acetic anhydride. However, upon attempting to prepare this acid in the present work, by a Knoevenagel condensation between malonic acid and 5-nitrofurfural, only tars were obtained. Therefore, the nitro acid was prepared by nitration of 2-furanacrylic acid in acetic anhydride.[4]

5-Nitro-2-furanacryloyl chloride was prepared with phosphorus pentachloride[5] or phosphorus trichloride, but thionyl chloride was not applicable. Ethyl 5-nitro-2-furanacrylate was prepared by the nitration of ethyl 2-furanacrylate[4] which was prepared by a Claisen condensation of furfural and ethyl acetate.[6]

The halo-5-nitro-2-furanacrylanilides prepared in the present work are presented in Table I. 2′,4′-Dichloro-5-nitro-2-furanacrylanilides has not been previously prepared.

(4) H. Gilman and G. F. Wright, *J. Am. Chem. Soc.*, **52**, 2550 (1930).

(5) K. Matsumoto, R. Ueno, and M. Ueno, Jap. Patent 2667 (1950).

(6) H. Gilman, R. E. Brown, and H. L. Jones, *Iowa State Coll. J. Sci.*, **2**, 317 (1928).

EXPERIMENTAL

Reagents. 2-Furanacrylic acid was purchased from the Eastman Kodak Co., Rochester, N. Y., and a sample of 5-nitrofurfural was obtained from the Norwich Pharmacal Co., Norwich, N. Y.

Ethyl 2-furanacrylate was prepared by the Claisen condensation from furfural and ethyl acetate[6] to give the desired ester, b.p. 111–114°/10 mm. which was redistilled at 97–99°/4 mm. (lit.[7] b.p. 120–121°/17 mm.).

Ethyl 5-nitro-2-furanacrylate was prepared by nitrating ethyl 2-furanacrylate in acetic anhydride[4] to give a pure product, m.p. 123.5–124° (lit.[4] m.p. 123°).

Halo-5-nitro-2-furanacrylanilides (attempts by ester-haloaniline reaction). Attempts were made to react ethyl 5-nitro-2-furanacrylate with *p*-chloroaniline by: (1) allowing a chloroform solution of the reactants to stand for 6 days at room temperature; (2) heating the mixture in refluxing xylene and allowing any alcohol formed to be driven off; (3) heating the mixture at 120° for 20 hr. in dimethylformamide. However, in all of these experiments only the starting reagents were recovered.

Halo-5-nitro-2-furanacrylanilides (by the phosphorus trichloride method). Four g. (0.02 mole) of 5-nitro-2-furanacrylic acid and 6.0 g. (0.05 mole) of *p*-chloroaniline were intimately ground, mixed, and refluxed with 1.5 ml. of phosphorus trichloride and 35 ml. of benzene for 16 hr. The mixture was cooled and filtered and the residue suspended into 10% hydrochloric acid, 10% sodium carbonate, re-filtered, and washed. Crystallization from ethanol gave 3.9 g. (65% yield) of 4′-chloro-5-nitro-2-furanacrylanilide, m.p. 213–215° (lit.[8] 214°). Admixture with the material prepared by the Schotten-Baumann reaction caused no depression of its melting point.

Halo-5-nitro-2-furanacrylanilide (by the Schotten-Baumann procedure). In initial work, the intermediate acid chlorides had been isolated. However, it was found that neither the purity nor the yield of the product was deleteriously affected if the acid chloride reaction mixture were reacted directly with the aniline. Either phosphorus pentachloride or phosphorus trichloride could be used to make the acid chloride. However, thionyl chloride was not found to be effective.

The method described below was used for the preparation of all of the compounds in Table I.

One hundred g. (0.55 mole) of 5-nitro-2-furanacrylic acid, 167 g. of phosphorus pentachloride, and 1 l. of benzene were refluxed for 4 hr. This solution was diluted to 1160 ml. with benzene and 1067 ml. (equivalent to 0.51 mole of acid) were added over a 30-min. period to a rapidly stirred and cooled (ice) mixture of 100 g. (0.79 mole) of *p*-chloroaniline dissolved in 1300 ml. of benzene and 520 g. of sodium hydroxide

(7) I. Heilborn and H. M. Burnsbury, *Dictionary of Organic Compounds*, Eyre and Spottiswoode, London, 1953, p. 575.

(8) T. Takahoshi, H. Saikachi, S. Yoshima, and C. Mizuno, *J. Pharm. Soc. Japan*, **69**, 286 (1949).

dissolved in 2500 ml. of water. The mixture was stirred for 30 min. more and vacuum-filtered. The residue was suspended into 10% hydrochloric acid, refiltered, and washed with water to give, upon drying, 114 g. (76.5% yield) of 4′-chloro-5-nitro-2-furanacrylanilide, m.p. 212–213.5° (lit.,[8] m.p. 214°). A portion was crystallized from alcohol to give orange crystals, m.p., 216°.

Anal. Calcd. for $C_{13}H_9ClN_2O_4$: C, 53.34; H, 3.09. Found: C, 53.56; H, 3.14.

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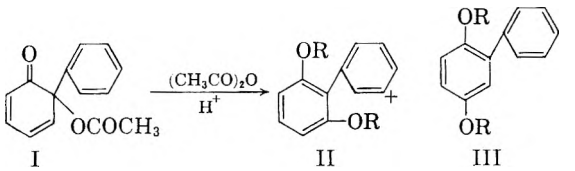
Dienone-Phenol Rearrangement of 2-Phenyl-*o*-quinolacetate[1]

H. BUDZIKIEWICZ AND W. METLESICS

Received January 12, 1959

In preceding papers[2,3] it has been shown that *o*-quinol acetates, when treated with acetic anhydride and a catalytic amount of concentrated acid or BF_3-etherate, are readily rearranged to acetylated phenols.

Under these conditions 2-methyl-*o*-quinol acetate yields 85% of 2,6-diacetoxytoluene and a trace of 2,5-diacetoxytoluene. In analogy to this result we expected to get mainly 2,6-diacetoxybiphenyl by subjecting 2-phenyl-*o*-quinol acetate (I) to this reaction:



I II III

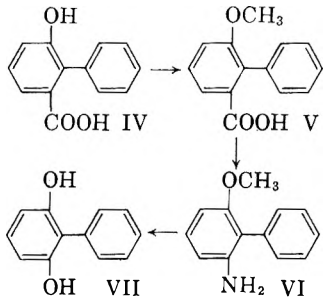
a. R = CH_3CO a. R = CH_3CO
b. R = H b. R = H

From the crude product an acetate, m.p. 91–93°, was obtained in 90% yield. Hydrolysis gave a phenol, m.p. 117–119°.

These melting points differ greatly from the figures given by Kubota and his co-workers[4] who described 2,6-dihydroxybiphenyl as having a melting point of 138° (m.p. of the diacetate 111°), a substance which we can hardly believe to be identical with our phenol IIb.

As infrared absorption, chromatographic behavior, and color reactions are consistent with the assumed structure of II, we have secured this result by an independent synthesis.

6-Hydroxybiphenyl-2-carboxylic acid (IV)[5] was transformed into 2,6-dihydroxybiphenyl as shown in the illustrated scheme.



The resulting phenol was identical with our rearrangement product IIb, as shown by mixed melting point and paper chromatography.

In the mother liquor of IIb some trace of a second phenol was found by paper chromatography. Color reaction and R_f value were the same as observed with a sample of 2,5-dihydroxybiphenyl[6] which had been prepared for comparison.

EXPERIMENTAL[7]

2-Phenyl-o-quinol acetate, I, was prepared by lead tetraacetate oxydation of 2-hydroxybiphenyl according to the directions of Wessely and his co-workers.[8]

Rearrangement of 2-phenyl-o-quinol acetate, I. Two-tenths of a gram of I was added in portions while stirring to a mixture of 2 ml. acetic anhydride and 2 drops of perchloric acid. The mixture was allowed to stand for 2 hr., then it was poured into 20 ml. of water. Having thus stood during the night, crystals had separated in 90% yield. The analytical sample, which was recrystallized from methanol and a mixture of ether and ligroin, resulted in 2,6-diacetoxybiphenyl, IIa, m.p. 91–93°, $\gamma_{max}^{CS_2}$ 1770 (C=O), 734, 696 (monosubstituted benzene ring), 762 (1,2,3-trisubstituted benzene ring).

Anal. Calcd. for $C_{16}H_{14}O_4$: C, 71.1; H, 5.2. Found: C, 71.3; H, 5.4.

Hydrolysis of the crude rearrangement product with a mixture of 10% sulfuric acid and methanol (1:1) yielded crystals which were recrystallized to give 2,6-dihydroxybiphenyl, IIb, m.p. 117.5–119°. IIb with an ethanolic solution of ferric chloride did not show any color reaction.

Anal. Calcd. for $C_{12}H_{10}O_2$: C, 77.4; H, 5.4. Found: C, 78.0; H, 5.5.

Paper chromatography of the products of hydrolysis was carried out by descending the upper phase of a mixture of benzene, glacial acetic acid, and water (4:1:5). IIb having been sprayed with diazotized sulfanilic acid solution and treated with ammonia vapors, formed a reddish brown spot. The mother liquors of IIb showed a second spot with the same R_f value and color reaction as observed with a sample of *2,5-dihydroxybiphenyl*, IIIb.

2,6-Dihydroxybiphenyl, VII, has been synthesized as follows:

6-Methoxybiphenyl-2-carboxylic acid, V. 6-Hydroxybiphenyl-2-carboxylic acid, IV,[5] treated with dimethylsulfate

(1) Paper III on Dienone-Phenol-Rearrangement of Quinols.

(2) F. Wessely and W. Metlesics, *Monatsh. Chem.*, **85**, 637 (1954).

(3) W. Metlesics, F. Wessely, and H. Budzikiewicz, *Tetrahedron* . . . (1959).

(4) B. Kubota, Y. Fujimura, K. Akashi, *Sci. Papers Inst. Phys. Chem. Research (Tokyo)*, **2**, 185 (1925); *Chem. Abstr.*, **19**, 2334 (1925).

(5) C. Graebe, P. Schestakow, *Ann.*, **284**, 316 (1894).

(6) W. Borsche, *Ann.*, **312**, 221 (1900).

(7) Infrared spectrum was measured using a Perkin-Elmer Model 21 spectrophotometer. Maxima are expressed in $cm.^{-1}$ Melting points are determined on a Kofler micro hot stage.

(8) F. Wessely, L. Holzer, and H. Vilcsek, *Monatsh. Chem.*, **83**, 1253 (1952).

formed V, which was then recrystallized from methanol m.p. 175–176°.

Anal. Calcd. for $C_{14}H_{12}O_3$: C, 73.7; H, 5.3. Found: C, 73.3; H, 5.4.

2-Amino-6-methoxybiphenyl, VI. Schmidt degradation of V was carried out according to the directions of Briggs and Lyttleton.[9] Concentrated sulfuric acid (0.15 ml.) was added to a mixture of 0.4 mmoles of V, 0.5 ml. of about 1*N* HN_3 in $CHCl_3$, and 1 ml. of $CHCl_3$ and the mixture was stirred until the evolution of gas had ceased. By treating the reaction mixture as described above a yellow oil was isolated being 2-amino-6-methoxybiphenyl, VI. It showed a positive reaction with Duke's reagent for primary amines. It was benzoylated by means of benzoyl chloride and pyridine to form a benzoate m.p. 106–107°.

Anal. Calcd. for $C_{20}H_{17}O_2N$: N, 4.6. Found: N, 4.5.

2,6-Dihydroxybiphenyl, VII. 2-Amino-6-methoxybiphenyl, VI, was diazotized and the diazonium salt decomposed in the usual way. By distillation 2-hydroxy-6-methoxybiphenyl could be isolated in the form of a yellowish oil which was cleaved by refluxing with a mixture of HBr (d = 1.38) and glacial acetic acid for 3 hr. to give white crystals of 2,6-dihydroxybiphenyl, VII, which recrystallized from a mixture of ether and ligroin. M.p. 118.5–119.5°, undepressed on admixture with the saponified rearrangement product. Identity was further proved by paper chromatography.

Acknowledgment. The authors wish to thank Prof. Dr. F. Wessely for his interest and helpful suggestions.

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(9) L. H. Briggs and J. W. Lyttleton, *J. Chem. Soc.* 421 (1943).

Reactions of Several 4-Pyrones Catalyzed by Potassium Acetate and Trifluoroacetic Acid

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Received January 13, 1959

In a previous communication[2] the reaction of aryl aldehydes with 2,6-dimethyl-4-pyrone in the presence of potassium hydroxide was described. The product in each of the cases reported was a vinyl derivative.

This Note is, in part, the description of the reaction of aryl aldehydes with 4-pyrones, some of which are methylated at positions 2 and 6, whereas others have these positions open or blocked with other groups. The only common denominator in the pyrones used in these experiments is that position 3 is unoccupied.

Since none of the various pyrones failed to react with the aryl aldehydes under the influence of fused potassium acetate, the point of ring attachment to form a secondary alcohol was probably position 3. The infrared absorption spectrum of the simplest compound of the I series (I_G), gives an absorption band at 3502 cm.$^{-1}$ indicating the presence of a hydroxyl radical. Chromanone formed unsaturated derivatives due to the presence of an extra ring hydrogen in position 3, which made possible the elimination of water. The compounds formed by the reaction of 4-pyrones with aldehydes under the catalytic influence of potassium acetate are given as I_{A-I} series of Table I.

A part of the study of the effect of certain catalysts on the reactive nature of 4-pyrones was the examination of the use of trifluoroacetic acid with acylating compounds on such substances.

It was found that the use of trifluoroacetic acid as a solvent would permit acyl halides to react with 4-pyrones in a clean reaction giving good yields in a short reaction time. The product was not contaminated with large amounts of polymeric substances as was encountered in some of the preparations by the zinc chloride method.[2,3]

Benzoylation of kojic acid diacetate gave the compound II_B which was quite different in its physical constants from 2-acetoxymethyl-5-acetoxy-6-benzoyl-4-pyrone which had been prepared earlier.[4] The fact that these two compounds are different means that the point of the attachment of the benzoyl group to the pyrone ring is position 3 when kojic acid diacetate is acylated under the influence of trifluoroacetic acid.

In order to prove that II_B has the benzoyl group in position 3 it was postulated that such a compound would form a pyronopyrone[5] under the rearranging and cyclizing influence of fused potassium acetate and acetic anhydride, since no such compound should be formed from 2-acetoxymethyl-5-acetoxy-6-benzoyl-4-pyrone.

Unfortunately the cyclized product from II_B was a liquid. Efforts to purify the compound by distillation have been unsuccessful.

Compound II_F has been reported previously[6] elsewhere but the method gave a polymeric mixture. The above procedure gave superior results in every respect.

Compound II_C was chosen as representative of the II_{A-G} series so the malononitrile derivative and the 2,4 dinitrophenylhydrazone of the pyridone of II_C were prepared as proof of the ketonic nature of the substances formed during the reaction.

EXPERIMENTAL[7]

Preparation of compounds of I_{A-I} series. One-tenth mole of the aldehyde was mixed with 0.1 mole of the pyrone and 0.1 mole of powdered fused potassium acetate in a 500-ml. flask and the mixture was heated for 2 hr. at 120–130° in a

(1) The person to whom all communications concerning this article are to be directed.

(2) L. L. Woods, *J. Am. Chem. Soc.*, **80**, 1440 (1958).

(3) L. L. Woods, *J. Org. Chem.*, **22**, 341 (1957).

(4) L. L. Woods, *J. Am. Chem. Soc.*, **74**, 1105 (1952).

(5) L. L. Woods, *J. Org. Chem.*, submitted for publication.

(6) L. L. Woods, *Texas Jour. Sci.*, **11**, 28 (1959).

(7) All analyses were performed by Dr. Carl Tiedcke, Teaneck, N. J. All melting points were determined on a Fisher-Johns apparatus.

TABLE I

Sample No.	Pyrone	Aldehyde	M.P.	Crude Yield, %	Formula	Calculated				Found			
						Carbon	Hydrogen	Nitrogen	Chlorine	Carbon	Hydrogen	Nitrogen	Chlorine
I_A	Chromanone[a]	Benzaldehyde	105–106	78	$C_{16}H_{12}O_2$	79.61	5.59			79.53	5.39		
I_B	Chromanone	*m*-Nitrobenzaldehyde	145–146	100	$C_{16}H_{11}NO_4$	68.32	3.94	4.98		68.01	4.14	4.72	
I_C	Kojic acid	Benzaldehyde	158	100	$C_{13}H_{12}O_5$	62.90	4.46			63.44	4.67		
I_D	α-Chloro-α-deoxy-kojic acid	Benzaldehyde	188.5	100	$C_{13}H_{11}ClO_4$	58.52	4.15		13.29	58.14	3.89		12.89
I_E	2,6-Dimethyl-4-pyrone	Salicylaldehyde	244–dec.	65	$C_{14}H_{14}O_4$	68.28	5.73			68.06	5.49		
I_F	Chromanone	Salicylaldehyde	156–157	90	$C_{16}H_{12}O_3$	76.17	4.43			76.08	4.25		
I_G	2,6-Dimethyl-4-pyrone	*m*-Nitrobenzaldehyde	95	74	$C_{14}H_{13}NO_5$	61.08	4.76	5.08		60.88	4.55	5.37	
I_H	Chromanone	*o*-Chlorobenzaldehyde	115–116	69	$C_{16}H_{11}ClO_2$	70.98	4.09		13.09	70.79	4.09		13.21
I_I	Chromanone	Phthalic anhydride	229	91	$C_{17}H_{12}O_5$	68.91	4.08			68.70	4.22		

[a] Benzodihydropyrone.

TABLE II

Sample No.	Pyrone	Acyl Derivative Used	Crude Yield, %	M.P.	Formula	Calculated				Found			
						Carbon	Hydrogen	Sulfur	Chlorine	Carbon	Hydrogen	Sulfur	Chlorine
II_A	Kojic acid diacetate	*p*-Tolyl chloride	100	115–116	$C_{15}H_{16}O_7$	62.78	4.68			62.84	4.55		
II_B	Kojic acid diacetate	Benzoyl chloride	83	143	$C_{17}H_{14}O_7$	61.81	4.27			61.59	4.20		
II_C	2,6-Dimethyl-4-pyrone	Benzoyl chloride	93	98	$C_{14}H_{12}O_3$	73.67	5.29			73.35	5.09		
II_D	Chromanone	Benzoyl chloride	91	97–98.5	$C_{16}H_{12}O_3$	76.17	4.79			76.34	4.58		
II_E	Kojic acid diacetate	Acetyl chloride	50	138	$C_{12}H_{12}O_7$	53.73	4.50			53.38	4.58		
II_F	2,6-Dimethyl-4*H*-pyran-4-thione	Benzoyl chloride	100	96–97	$C_{14}H_{12}SO_2$	68.82	4.94	13.12		68.42	4.70	13.46	
II_G	2-Chloromethyl-5-acetoxy-4-pyrone	Benzoyl chloride	43	103–104	$C_{15}H_{11}ClO_5$	58.74	3.61		11.53	58.38	3.64		11.91

Fisher Hi-Temp oil bath. The resulting melt was diluted with about 100 ml. of water to which 10 ml. of concentrated hydrochloric acid had been added, chilled and filtered. The purified compound was obtained by recrystallizing the crude product twice from absolute ethanol or heptane. Compound I_I was prepared by heating the melt at the above temperature for 21 hr.

Preparation of the phenacyl derivative of I_I. One g. of I_I and 0.5 g. of sodium bicarbonate were mixed in 5 ml. of water. When the reaction had subsided 40 ml. of absolute ethanol and 1 g. of phenacyl bromide were added. The mixture was refluxed for 1 hr. and then poured into about 200 ml. of water containing 10 ml. of concentrated hydrochloric acid. The precipitate was filtered off, dried in air, and recrystallized twice from absolute ethanol, m.p. 229–231°.

Anal. Calcd. for $C_{25}H_{18}O_6$: C, 72.45; H, 4.37. Found: C, 72.64; H, 4.15.

Preparation of compounds of II_{A-G} *series.* One-tenth mole of the pyrone was dissolved in 25 ml. of redistilled trifluoroacetic acid; to this mixture was added, all at once, 0.1 mole of the acyl halide. After thoroughly mixing the reactants the mixture was refluxed for 1 hr., during which time large volumes of hydrogen chloride were evolved.

The reaction product, usually of a brown or purple color, was poured into about 150 ml. of water. The crystallized compound was filtered off, dried in air, and recrystallized several times from absolute ethanol or from boiling heptane.

Bis-malononitrile derivative of II_C. One g. of II_C was mixed with 10 ml. of acetic anhydride along with about 800 mg. of malononitrile, and the resulting solution was refluxed for 1 hr. The brown solution when poured into water precipitated a dark compound which when recrystallized twice from heptane melted at 193–194°.

Anal. Calcd. for $C_{20}H_{12}N_4O$; N, 17.27. Found: N, 17.02.

2,4-Dinitrophenylhydrazone of pyridone of II_C. Six g. of II_C was dissolved in 50 ml. of absolute ethanol and then 10 ml. of concentrated ammonium hydroxide solution was added. The solution was chilled overnight in the refrigerator. A yellow precipitate of the pyridone was obtained, 2 g. of which were reacted with 2 g. of 2,4-dinitrophenylhydrazine in 100 ml. of boiling absolute ethanol. The solution was filtered after 5 min. Cooling the solution permitted an orange precipitate to collect. The compound was recrystallized once from ethanol, m.p. 201–202°.

Anal. Calcd. for $C_{20}H_{17}N_5O_5$: N, 17.20. Found: 17.34.

Acknowledgment. The authors wish to acknowledge with thanks the financial support of this research project by the Robert A. Welch Foundation.

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New Synthesis of Tetrachlorothiophene

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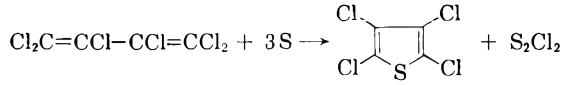
Received January 15, 1959

Tetrachlorothiophene has heretofore been prepared by the chlorination of thiophene, by methods involving the dehydrochlorination or dechlorination of one or more chlorine-addition intermediates.[1]

In the synthesis described herein,[2] tetrachlorothiophene is prepared by the interaction of hexachlorobutadiene and elemental sulfur. Formation of the thiophene ring is effected by replacement of two of the terminal chlorine atoms of hexachlorobutadiene by sulfur. The chlorine appears as sulfur monochloride. Both products are produced in essentially quantitative yields as defined by the following stoichiometry.



EXPERIMENTAL

A solution of 11,740 g. (45 moles—200% excess) of hexachlorobutadiene and 1443 g. (45 moles) of sulfur was heated at reflux (205–240°) under a 100 cm. distillation column packed with 1/8 inch glass helices. As sulfur monochloride formed it was removed at the top of the column. During 13 hr. 1946 g. (14.4 moles) of sulfur monochloride was distilled off. The system was then put under 7.8 mm. of vacuum and after the excess hexachlorobutadiene containing some tetrachlorothiophene was removed, 2704 g. (12.2 moles, 81% yield) of tetrachlorothiophene was taken off at 91–94°. The latter portion of this fraction gave the following analysis.

Anal. Calcd. for C_4Cl_4S: Cl, 63.91; S, 14.45. Found: Cl, 63.7; S, 14.4.

The total yield of tetrachlorothiophene as calculated from infrared analysis of all distillation fractions was 99%. The product melted at 29.5–29.7° after crystallization from methanol.

In a second experiment the excess of hexachlorobutadiene was reduced to 10%. The sulfur was added in portions to the hexachlorobutadiene during the reaction in order to avoid the presence of undissolved sulfur. In this case the product was redistilled to remove traces of sulfur chloride. A 94.1% yield of tetrachlorothiophene was obtained, of which 76% was isolated as 99.5–99.7% pure product.

HOOKER CHEMICAL CORPORATION
RESEARCH AND DEVELOPMENT DEPARTMENT

Studies in *p*-Cymene, IV. Some *N,N'*-Diarylthioureas

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Received January 20, 1959

This study is a continuation of the work of LeConte and Chance[2] for the purpose of preparing new *N,N'*-diarylthioureas to be used in the antici-

(1) H. D. Hartough, *Thiophene and its Derivatives*, (The Chemistry of Heterocyclic Compounds series, A. Weissberger, ed.) Interscience Publishers, Inc., New York, 1952, pp. 180, 185.

(2) Further experimental data are included in a pending U. S. patent.

(1) (a) Present address: East Carolina College, Greenville, N. C. (b) An abstract of a thesis submitted by William N. Cannon to the Graduate School, University of Georgia, in partial fulfullment of the requirements for the degree of Master of Science. Present address: Eli Lilly & Co., Indianapolis, Ind.

(2) J. N. LeConte and L. P. Chance; *J. Am. Chem. Soc.*, **71**, 2240 (1949).

TABLE I

ARYL 5-HYDROXY-*p*-CYMYLTHIOUREAS AND DERIVED PRODUCTS

	Yield, %	M.P.	Formula	Sulfur Calcd.	Sulfur Found
N,N'-di-(4-hydroxy-5-isopropyl-2-methylphenyl)-thiourea	70	232–233°	$C_{21}H_{28}O_2N_2S$	8.60	8.45
5-Hydroxy-2-*p*-cymyl isothiocyanate	68.5	164–166° 3 mm. (b.p.)	$C_{11}H_{13}ONS$	15.45	15.76
5-Hydroxy-2-*p*-cymyl phenylthiosemicarbazide	84	180–181°	$C_{17}H_{21}ON_3S$	10.15	9.87
o-Tolyl-2-(5-hydroxy-*p*-cymyl)thiourea	51	187–188°	$C_{18}H_{22}ON_2S$	10.19	10.35
m-Tolyl-2-(5-hydroxy-*p*-cymyl)thiourea	71	193°			10.13
p-Tolyl-2-(5-hydroxy-*p*-cymyl)thiourea	35	174–175°			10.15

pated preparation of substituted quinolines by the method of Dziewonski and Moszew.[3]

N,N'-di-(4-hydroxy-5-isopropyl-2-methylphenyl)thiourea was made by standard procedure from 2-amino-5-hydroxy-*p*-cymene and carbon disulfide, then split with acetic anhydride to form 5-hydroxy-2-*p*-cymyl isothiocyanate and 2-acetamino-5-hydroxy-*p*-cymene. There was no evidence of the formation of a guanidine compound. When isolated the isothiocyanate reacted with 2-amino-5-hydroxy-*p*-cymene to reform the original thiourea, proved by the mixed melting point method. The isothiocyanate also was reacted with phenylhydrazine to form 5-hydroxy-2-*p*-cymyl phenylthiosemicarbazide. A sulfur analysis indicated mole to mole reaction in contradiction to the findings of Otterbacher and Whitmore,[4] who found that two moles of isothiocyanates react with one of phenylhydrazine.

The preparations of *N*-(*o*-, *m*-, and *p*-)tolyl-*N'*-4-hydroxy-5-isopropyl-2-methyl-phenylthioureas were accomplished by the reaction of 2-amino-5-hydroxy-*p*-cymene with the respective *o*-, *m*-, and *p*-tolyl isothiocyanates. Results are found in Table I. The sulfur content of new compounds was determined by the Parr bomb method. All melting points are uncorrected.

EXPERIMENTAL

I. Preparation of N,N'-di-(4-hydroxy-5-isopropyl-2-methylphenyl)thiourea and its derivatives. 2-Amino-5-hydroxy-*p*-cymene, 200 g. (1.21 moles), was dissolved in 400 ml. of absolute ethanol and the resulting solution added to a mixture of 228 g. (3.0 moles) of carbon disulfide and 5 g. of solid potassium hydroxide in a 2-l. flask equipped with a reflux condenser. The reaction flask was heated on a water bath. A soda-lime trap was attached to the condenser to absorb the hydrogen sulfide liberated in the reaction. The reaction mixture was refluxed for 22 hr. when hydrogen sulfide ceased to be evolved. The solution was concentrated to about half its original volume, and on cooling a heavy separation of white crystals was observed. These were filtered and immediately washed with cold alcohol. Several recrystallizations from ethanol were necessary to obtain a sample for analysis. However, the crude product proved satisfactory in preparing the isothiocyanate.

(3) K. Dziewonski and J. Moszew, *Roczniki Chem.*, **12**, 482, 925 (1932); *Chem. Abstr.*, **27**, 3937 (1933); **28**, 152 (1934).

(4) T. Otterbacher and F. C. Whitmore, *J. Am. Chem. Soc.*, **51**, 1909 (1929).

5-Hydroxy-2-p-cymyl isothiocyanate. A mixture of 130 g (0.35 mole) of the thiourea and 62 g. (0.6 mole) of acetic anhydride were mixed in a 500-ml. flask equipped with a reflux condenser. The solution of the thiourea was complete when warmed. The solution was refluxed for 5 min. and poured into 400 ml. of hot water. A heavy dark oil settled out. The mixture was steam distilled, the distillate extracted with ether, dried overnight over anhydrous sodium sulfate, ether evaporated, and the product distilled under reduced pressure. The main fraction was a pale, straw-colored oil boiling at 164–166°/3 mm. No boiling point could be determined at atmospheric pressure because of decomposition.

5-Hydroxy-2-p-cymyl phenyl thiosemicarbazide. A mixture of 10 g. (0.05 mole) of 5-hydroxy-2-*p*-cymyl isothiocyanate, 5 g. (0.05 mole) phenylhydrazine and 25 ml. absolute ethanol was made in a 50 ml. Erlenmeyer flask. Heat was evolved immediately. After cooling slightly, the reaction mixture was warmed on a water bath for 20 min. The white crystals which separated on cooling were filtered, washed with cold ethanol, and recrystallized from hot ethanol.

II. Preparation of the N,N'-tolyl(hydroxy-p-cymyl)thioureas. The tolylisothiocyanates were prepared in the usual way from their symmetrical thioureas. Mixtures of each were made with 34 g. of the isothiocyanate, 37 g. of 2-amino-5-hydroxy-*p*-cymene (one to one mole ratio) in 200 ml. of absolute ethanol. The resulting solutions were refluxed for 2 hr., concentrated to half their original volumes by distilling off part of the ethanol. As the solutions cooled, the white crystalline products separated, were filtered and recrystallized from ethanol. The *m*-tolylisothiocyanate reacted on contact with the amine and refluxing was unnecessary.

SUMMARY

5-Hydroxy-2-*p*-cymylisothiocyanate was prepared and from it several new *N,N'*-diarylthioureas were made and characterized.

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Reactions of Olefin-Mercuric Acetate Addition Compounds with Ethyl Acetoacetate in the Presence of Alkylating Catalyst

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Received January 22, 1959

The new reactions which form aralkyl acetates through intermediate mercurials ($ArCH_2CH_2HgZ$)

by the reaction of ethylene–mercuric acetate addition compound with aromatic compounds[1,2] have been extended to the case of ethyl acetoacetate in place of the aromatics.

In the presence of boron trifluoride–acetic acid complex, the reaction of ethylene gives ethyl α-(2-acetoxyethyl)acetoacetate (I). This structure was established by the ketonic hydrolysis of the β-ketoester group and by the simultaneous hydrolysis of the other ester group to give 5-hydroxy-2-pentanone. The best yield was obtained by keeping the reaction mixture at a lower temperature for several hours and then at 70–75° for about 1 hr. Prolonged reaction at 70–75° resulted in a lower yield, despite the increased formation of free mercury, because a high-boiling tarry material was formed.

Ethyl α-(2-chloromercuryethyl)acetoacetate (II) was isolated as an intermediate of the reaction, when the reaction product under milder condition was treated with an aqueous sodium chloride solution. The procedure of the structure determination of this new compound is demonstrated by the following reaction scheme (a).

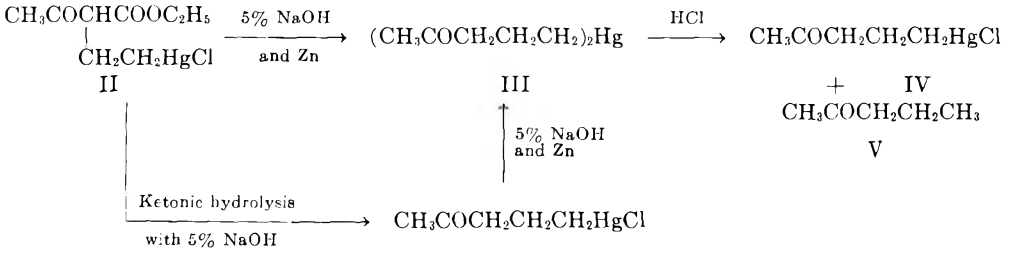
temperature of 90–95° where the free mercury and I are formed from the intermediate mercurial.

The reaction of propylene gives ethyl α-acetyl-β-acetoxymethylbutyrate (VI), whose structure was established by the hydrolysis to 4-methyl-5-hydroxy-2-pentanone. This shows that ethyl acetoacetate reacts with the central carbon of propylene, while the aromatic compounds reacted with the terminal carbon of the same olefin.[2]

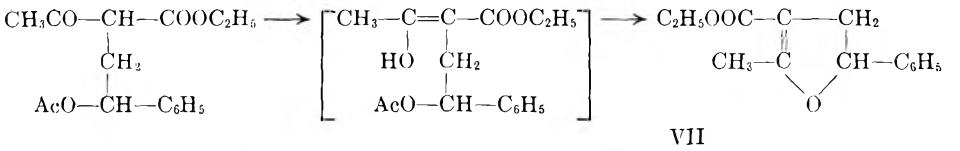
The reaction of styrene gives a product which is thought to be ethyl 2-methyl-(4 or 5)-phenyl-4,5-dihydro-3-furoate (VII or VII′). The following two reaction schemes (b and c) appear to be possible, since the reaction of the styrene-mercuric acetate addition compound with anisole gave a mixture of 1-phenyl-2-(*p*-methoxyphenyl)- and 2-phenyl-2-(*p*-methoxyphenyl)ethylmercury salt.[2]

This compound showed negative tests for carbonyl group and positive tests for double bond and was analyzed correctly for VII or VII′. Alkaline hydrolysis gave an acid which is thought to be 2-methyl-(4 or 5)phenyl-4,5-dihydro-3-furoic acid and was analyzed correctly for it. Alkaline oxidation of VII (or VII′) with potassium permanganate gave

(a)

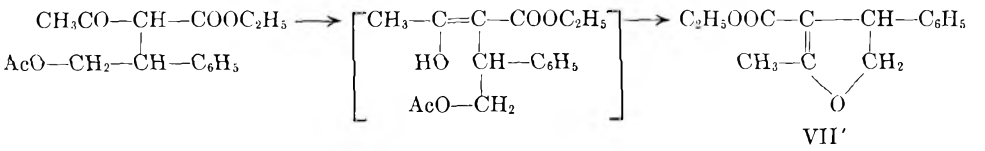


(b)



or

(c)



The results mentioned above are obtained with boron trifluoride as the catalyst. Perchloric acid which has been a successful catalyst in the series of this reaction[1,2] gave the same result in the experiment of the isolation of the intermediate mercurial. This catalyst, however, failed to give the final product I, because I and ethyl acetoacetate were decomposed with perchloric acid at the higher

benzoic acid only. Several attempts to determine the position of the phenyl group 4 or 5 were unsuccessful. However, the fact that no dihydrofuran derivatives are formed in the cases of ethylene and propylene suggests strongly that the phenyl is attached to the position of 5, because 5-phenyldihydrofuran formation is expected to be much easier than that of 4-phenyl derivative.

(1) K. Ichikawa, S. Fukushima, H. Ouchi and M. Tsuchida, *J. Am. Chem. Soc.*, **80**, 6005 (1958).

(2) K. Ichikawa, S. Fukushima, H. Ouchi and M Tsuchida, *J. Am. Chem. Soc.* **81**, 3401 (1959).

EXPERIMENTAL

Ethyl α-(2-acetoxyethyl)acetoacetate (I). At 18–20°, ethylene was introduced into the mixture of mercuric acetate (96 g.) and acetic acid (90 ml.) with good stirring until the mercuric ion could no longer be detected by sodium hydroxide solution. To this solution, ethyl acetoacetate (78 g.) and then boron trifluoride–acetic acid complex (51 g.) were added under continued stirring. The reaction mixture was kept at 30–32° for 5 hr. and then at 70–75° for 1 hr. After separating the metallic mercury (38 g., 63% of theor.) formed, the reaction mixture was diluted with water (500 ml.) and then extracted with benzene (400 ml.). The benzene extract was washed with saturated salt solution and then dried over anhydrous sodium sulfate. Distillation gave a crude I (24 g., yield, 37%, b.p. 120–130°/5 mm.). After a redistillation, I (22 g., b.p. 115–116°/2.5 mm., n_D^{20} 1.4403, d_D^{20} 1.0924) was obtained.

Anal. Calcd. for $C_{10}H_{16}O_5$: C, 55.54; H, 7.46. Found: C, 55.61; H, 7.43.

When the reaction mixture of the same composition as in the case above was kept at 70–75° for 1.5 hr. from the beginning of the reaction, a lower yield of I (21%) was obtained, despite the increased formation of free mercury (75% of theor.).

Hydrolysis of I *to 5-hydroxy-2-pentanone.* At 30–32°, I (18.3 g.) was dissolved in 5% aqueous sodium hydroxide solution (90 ml.) under good stirring for 4 hr. About 5 g. of I remained insoluble and was extracted off with ether. The water layer was allowed to stand at room temperature (30–32°) for 8 days and then was acidified with dilute hydrochloric acid. From this water solution, a crude 2,4-dinitrophenylhydrazone of 5-hydroxy-2-pentanone (15.3 g., m.p. 140–142°) was obtained. After a recrystallization from ethanal, the m.p. was 148–149° (reported[3] 150°).

Anal. Calcd. for $C_{11}H_{14}N_4O_5$: C, 46.81; H, 5.00; N, 19.85. Found: C, 46.85; H, 5.04; N, 20.00.

Ethyl α-(2-chloromercuryethyl)acetoacetate (II). To the acetic acid solution of ethylene–mercuric acetate addition compound which was prepared from acetic acid (90 ml.), mercuric acetate (96 g.) and ethylene, ethyl acetoacetate (195 g.), and then boron trifluoride–acetic acid complex (51 g.) were added under good stirring at below 20°. After a period of 4 hr. at 20°, the reaction mixture was poured into water (600 ml.). To this solution, 10% salt solution (200 ml.) was added under stirring. The resulting heavy oil was separated from the water layer. The water layer was extracted with benzene. This benzene extract was combined with the heavy oil mentioned above, washed with saturated salt solution, and then dried over anhydrous sodium sulfate. After the recovery of benzene and ethyl acetoacetate under reduced pressure, a heavy viscous oil (II) (106 g.) was obtained as a residue.

Conversion of II *to bis(2-pentanon-5-yl)-mercury* (III). II (93 g.) was dissolved into 5% aqueous sodium hydroxide solution (350 ml.). This solution was warmed up to 95° and then zinc dust (40 g.) was added in several portions during a period of 1.5 hr. under stirring. After the addition of zinc dust, the stirring was continued for 10 min. A resulting heavy oil was separated from the reaction mixture and combined with the ether extract of the water layer. This was washed with saturated salt solution and then dried over anhydrous sodium sulfate. Distillation gave a heavy liquid (III) (25.5 g., b.p. 167–169°/3 mm.) (Hg analysis; Calcd. for $C_{10}H_{18}HgO_2$ 54.09; found, 54.22.).

Conversion of III *to 5-chloromercury-2-pentanone* (IV) *and 2-pentanone* (V). III (5.2 g.) was dissolved into concentrated hydrochloric acid (8 ml.) at room temperature and then was kept at 60–70° for several minutes. By adding water (40 ml.) to this solution white plates (IV) (3.9 g., m.p. 74.5–75°) were obtained. Recrystallization from hot water did not change the melting point. Hg analysis: Calcd. for C_5H_9ClHgO 62.46; found 62.20. The water solution which was separated from IV was distilled under reduced pressure to almost dryness. From the distillate, a crude 2,4-dinitrophenylhydrazone of 2-pentanone (V) (3.5 g., m.p. 139–140°) was obtained. Recrystallization from a mixture of alcohol and ethyl acetate gave the m.p. 144.5–145° (reported[3] 144°).

Anal. Calcd. for $C_{11}H_{14}N_4O_4$: 49.62; H, 5.30; N, 21.04. Found: C, 49.60; H, 5.43; N, 21.24.

Conversion of II *to 5-chloromercury-2-pentanone* (IV′). II (87 g.) was dissolved into 5% aqueous sodium hydroxide solution (450 ml.) and was kept 25–30° under stirring for 4 hr. After being acidified with 18% hydrochloric acid, the reaction mixture was warmed on a steam bath for about 30 min. until the evolution of carbon dioxide was complete. By cooling the reaction mixture in an ice bath, a crude 5-chloromercury-2-pentanone (IV′) (55 g., m.p. 70–73°) was obtained. Recrystallization from hot water gave white plates, m.p. 74.5–75°. Mixed melting point with IV showed no depression.

Conversion of IV′ *to* III. By the same method as in the case of II, IV′ (27 g.) was reduced with zinc dust (12 g.) and 5% aqueous sodium hydroxide solution (100 ml.). Mercury content of the resulted heavy oil (III) (10.2 g., b.p. 162–163°/2.5 mm.) was 53.47% (calcd., 54.09%). Treatment of this product (8.5 g.) with concentrated hydrochloric acid (12 ml.) resulted in the formation of IV (4.5 g., m.p. 74.5–75°). Mixed melting point with IV′ showed no depression.

Ethyl α-acetyl-β-acetoxymethyl butyrate (VI). Under the conditions similar to the case of ethylene, the reaction of propylenemercuric acetate addition compound with ethyl acetoacetate gave VI (18 g., yield, 26%, b.p. 108.5–110.5°/2.5 mm., n_D^{20} 1.4425, d_D^{20} 1.0648).

Anal. Calcd. for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88. Found: C, 57.39; H, 8.08.

Hydrolysis of VI *to 4-methyl-5-hydroxy-2-pentanone.* VI (2.5 g.) was dissolved into 5% aqueous sodium hydroxide solution (22 ml.) and was kept at room temperature (30–32°) for 8 days. After a small amount of unreacted VI was extracted with ether, the water layer was acidified with dilute hydrochloric acid. From this solution, a crude 2,4-dinitrohydrazone of 4-methyl-5-hydroxy-2-pentanone (2.6 g., m.p. 98–104°) was obtained. The melting point was 104–105.5° after a recrystallization from 80% ethanol (reported[4] 104°).

Anal. Calcd. for $C_{12}H_{16}N_4O_5$: C, 48.64; H, 5.44; N, 18.91. Found: C, 48.61; H, 5.40; N, 19.02.

Ethyl 2-methyl-5-phenyl-4,5-dihydro-3-furoate (VII). Under the same conditions as in the case of ethylene, except that 155 g. of acetoacetate was used and the final reaction temperature was 77–81° for 50 min., the reaction of styrene–mercuric acetate addition compound gave a liquid (24 g.) which is thought to be VII, b.p. 128–130°/3 mm., n_D^{20} 1.5285, d_D^{20} 1.1008.

Anal. Calcd. for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.10; H, 6.97.

Hydrolysis of VII *to 2-methyl-5-phenyl-4,5-dihydro-3-furoic acid.* VII (10 g.) was dissolved into 20% ethanolic potassium hydroxide solution (50 g.) and was heated on a steam bath under reflux for 7 hr. Ethanol was removed and then a small amount of water was added to the residue. An unreacted VII (about 4 g.) was extracted off with ether. The water layer was acidified with dilute hydrochloric acid. The resulting crystals were recrystallized from 80% ethanol to give white needles (2.3g.), m.p. 172.5° (with decomposition), which are thought to be 2-methyl-5-phenyl-4,5-dihydro-3-furoic acid.

Anal. Calcd. for $C_{12}H_{12}O_3$: C, 70.57; H, 5.92. Found: C, 70.54; H, 6.08.

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(3) R. Paul and S. Tchelitcheff, *Bull. soc. chim. France*, 418 (1953).

(4) J. Colonge and R. Gelin, *Bull. soc. chim. France*, 801 (1954).

Acknowledgment. The authors wish to express their appreciation to Sumitomo Chemical Co. for a financial support and to Mr. E. E. Daub for his help in English correction.

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Fluorination of Hexachlorobenzene with Antimony Pentafluoride

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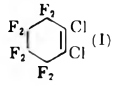
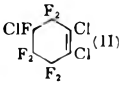
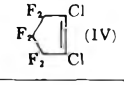
Received January 22, 1959

The reaction of hexachlorobenzene with antimonypentafluoride has been described in the literature,[1] but further work has shown some unreported facts. Care must be taken in heating the reaction mixture since at 160° there is a large evolution of heat which will cause loss of product unless cooling is used.

In the original procedure the only product described is I, *cf.* Table I, b.p. 111–113° and the yield is stated to be 44%. In addition to I, three other fluorinated materials have been recovered, their properties are listed below.

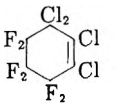
TABLE I

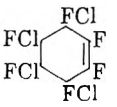
Compound	B.P.	d_4^{20}	n_D^{30}	Analyses Theor.	Analyses Found	Yield, %
 (I)	113°	1.729	1.3653	Cl 24.05	24.23	20–30
 (II)	140–1.8°	1.767	1.3995	Cl 34.10 C 23.11	33.71 24.07	20
 (III)	95°/63 mm.	1.793	1.4313	Cl 43.30 C 22.02	42.70 23.18	5
 (IV)	89–90°	1.642	1.3619	Cl 29.0	28.43	<1%

The purity of compounds I–III was checked by gas chromatography and structure determinations were made with the aid of infrared and nuclear magnetic resonance[2] measurements.

The following basis was used for structural assignments. In compounds I–III a single infrared absorption band was found at 6.15 μ and was assigned to the CCl=CCl grouping. Compounds with F atoms attached to the doubly bonded carbon atoms absorb at higher frequencies as has been observed with a number of compounds. The NMR absorption for I shows two different kinds of F atoms in agreement with the formula assigned and oxidation with $KMnO_4$ gives the expected perfluoroadipic acid.[1] The compound II was shown to have four different kinds of F atoms and the boiling point, refractive index, and density show the proper incremental changes.

The highest boiling material (III) was assigned the structure shown since NMR indicates three types of fluorine each containing two F atoms. Other structures for III which are unlikely but cannot be ruled out by NMR are as follows:


A


B

In both of these cases one would expect to find a signal very near the high field reference line from either C=CF or CF_2—CF_2—CF_2 groupings. However, the 6.15μ CCl=CCl band definitely rules out structure B.

Also isolated was a very small amount of IV.[3] Further identification was made by chlorinating this material under the influence of ultraviolet light to give a solid m.p. 138–145°, Cl 43.4%. The reported product of the chlorination is $C_5F_6Cl_4$, m.p. 151°, Cl 44.9%. Comparison of the infrared spectrum of IV with the authentic $C_5F_6Cl_2$ was also in agreement.

It was first assumed that the source of IV was the presence of a cyclopentene impurity in the starting material. An examination was made for impurities in the starting C_6Cl_6 by extraction with

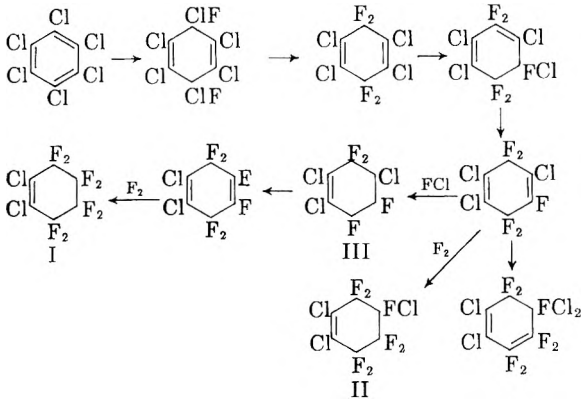
(1) E. T. McBee, P. A. Wiseman, and G. B. Bachman, *Ind. Eng. Chem.*, **39**, 415 (1947).

(2) Performed by Varian Associates, Palo Alto, Calif.

(3) A. L. Henne and W. J. Zimmerschied, *J. Am. Chem. Soc.*, **67**, 1265 (1945).

boiling CCl_4. The undissolved residue was discarded and the filtrate partially evaporated to deposit C_6Cl_6 on cooling. An infrared spectrum was run on this filtrate using a pure saturated solution of C_6Cl_6 in CCl_4 as a balance and unknown bands were found at 6.92 (m), 7.15 (s), 7.52 (m), 7.75 (w), 8.55 (m), 8.96 (w), 9.22 (w), 9.43 (w), and 14.71μ(s). An authentic sample of C_6Cl_5H in CCl_4 gave bands at 7.15 (s), 7.48 (s), 7.65 (w), 8.16 (w), 8.28 (w), 8.55 (s), 9.22 (m), and 14.68μ (s). Spectra were run of hexachlorocyclopentene and octachlorofulvene but neighter of these matched the unknown lines. Characteristic bands of octachlorocyclopentene listed in the literature[4] were also absent from this spectra. Therefore, at least one of the impurities present is C_6Cl_5H with still smaller amounts of other materials. The mechanism of the formation of IV is not known but must must come from a benzene starting material.

A mechanism for the formation of the cyclohexene compounds is shown below and is based on the usual addition-elimination mechanism found in fluorination. The conjugation of the double bond is similar to that suggested by Latif[5] in connection with the fluorination of octachlorocyclopentene.



During the initial phase of the fluorination, there will be relatively little Cl present, but as more and more SbF_3Cl_2 is produced there will be a sufficient amount present to allow chlorination of the starting material to produce $C_6F_6Cl_4$. This is the basis for the FCl addition to the intermediate $C_6F_6Cl_2$. In these reactions it is not known whether FCl or F_2 is added as a unit or by a stepwise mechanism involving SbF_4 + F and SbF_3Cl + Cl and no differentiation is made.

Acknowledgment. The author wishes to thank the Office of Naval Research for partial support of this work and Dr. A. E. Pavlath for helpful discussions on the mechanism of fluorination.

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(4) H. E. Ungnade and E. T. McBee, *Chem. Revs.*, **58**, 307 (1958).

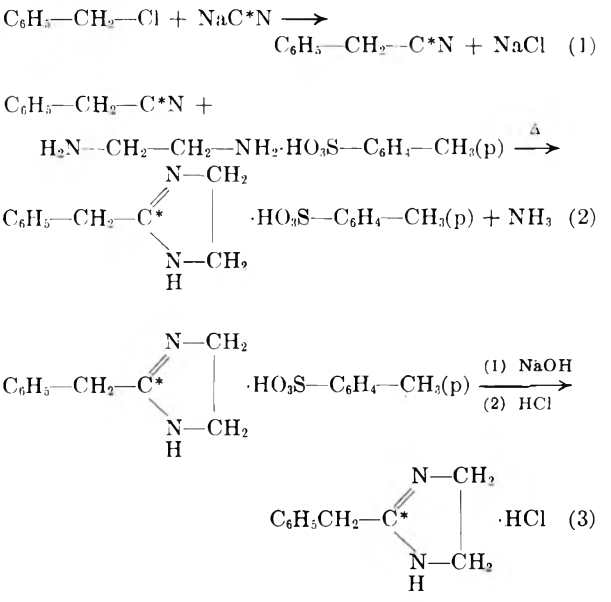
(5) K. A. Latif, *J. Indian Chem. Soc.*, **30**, 525 (1953).

Synthesis of Isotopically Labeled Medicinals. II. 2-Benzylimidazoline-2-C^{14} Hydrochloride

J. B. ZIEGLER AND A. C. SHABICA

Received January 27, 1959

2-Benzylimidazoline hydrochloride[1] is an effective peripheral vasodilating agent and adrenergic blocking agent. A sample of this substance labeled with carbon 14 was required for fate studies in the mammalian body. Although it is manufactured commercially by the condensation of benzyl cyanide and ethylenediamine base in the presence of carbon disulfide, this reaction proved to be unsuitable in our hands on a 10-mmol. scale; only dark colored oils yielding little or none of the desired product were obtained. The modification of Oxley and Short[2] (use of ethylenediamine as the mono-*p*-toluenesulfonate) was finally employed successfully on a micro scale. The complete synthesis took the following form.



Details of the fate of this labeled 2-benzylimidazoline hydrochloride in the rat have been published elsewhere,[3] although it was erroneously stated in that publication that the compound bore the carbon 14 label at the methylene group between the benzene and imidazoline rings.

As is customary, the synthesis was worked out in detail using inactive sodium cyanide before making the target run using the labeled sodium cyanide. Since our sample of labeled sodium cyanide contained sodium hydroxide to minimize loss of the

(1) Tolazoline CIBA = Priscoline^R.

(2) P. Oxley and W. F. Short, *J. Chem. Soc.*, 497 (1947).

(3) B. Century, *Proc. Soc. Exptl. Biol. Med.*, **92**, 518 (1956).

label as HCN through hydrolysis, a compensatory excess of benzyl chloride was employed in the synthesis of the labeled benzyl cyanide to react with the sodium hydroxide and to conserve the active cyanide. The crude active benzyl cyanide was used directly in the next step to avoid losses attendant upon purification, and an excess of ethylene diamine mono-*p*-toluenesulfonate was used in order to conserve the labeled nitrile.

EXPERIMENTAL

Benzyl C^{14}-cyanide. The labeled sodium cyanide[4] (0.10 g.; 2 mmol., specific activity = 20 μc./mg.), containing 0.08 g. (2 mmol.) of sodium hydroxide, was placed in a 50-ml., round bottomed, ground-joint flask and diluted with 0.40 g. (8 mmol.) of inactive sodium cyanide. To this mixture was added 0.5 ml. of water, 2.0 ml. of 95% ethanol, and 1.65 g. (1.51 ml.; 13 mmol.) of benzyl chloride. The mixture was heated under reflux for 4 hr. Anhydrous ether was added and the solution was dried over anhydrous sodium sulfate and filtered. Removal of solvent *in vacuo* left a residue of crude benzyl cyanide.

2-Benzylimidazoline-2-C^{14} hydrochloride. The crude benzyl cyanide from above was treated with 3.01 g. (13 mmol.) of ethylenediamine mono-*p*-toluenesulfonate[2] and the flask was fitted with an air condenser. The mixture was heated at 200° for 1 hr., during which time ammonia gas was evolved, and then allowed to cool to room temperature. The solid was dissolved in 5 ml. of water and the solution was made strongly alkaline with 30% sodium hydroxide solution, precipitating an oil. The oil was taken up in chloroform and this solution was washed well with water. After drying over anhydrous sodium sulfate, the solvent was removed *in vacuo*. The orange gum was dissolved in 1.6 ml. of absolute ethanol and 3.2 ml. of ethyl acetate was added. After saturation with hydrogen chloride gas, 15 ml. of ether was slowly added with shaking. After standing overnight at room temperature, the supernatant liquid was decanted from the reddish brown gum, and this was washed with fresh ether by decantation. It was dissolved in the minimum amount of absolute ethanol and the solution was filtered to remove a small amount of an insoluble contaminant, m.p. 285–300° (uncorr.). The filtrate was heated to boiling and ethyl acetate was slowly added until crystallization had begun. After chilling overnight in the refrigerator, the crystalline material was collected by filtration, washed with a little fresh 6:1 ethyl acetate–absolute ethanol, ethyl acetate, ether, and finally air-dried. The pinkish crystals weighed 0.87 g., m.p. 170–174°. A second crop was obtained by combining mother liquors, adding ether, and crystallizing the resulting gum from absolute ethanol–ethyl acetate. After two additional crystallizations from the same solvent system, an additional 0.15 g. of tan crystals, m.p. 170–172° (uncorr.), was obtained. The combined crops (1.02 g.) were given a final recrystallization from absolute ethanol–ethyl acetate, affording 0.89 g. (45% of theory based on sodium cyanide), m.p. 170–172° (uncorr.) (lit. gives 175°,[2] 168–170°,[5a] 174°[5b]).

Anal. Calcd. for $C_{10}H_{13}N_2Cl$: N, 14.25; Cl, 18.03. Found: N, 14.44; Cl, 18.27.

The specific activity of the product was found[3] to be 1 μc./mg.

RESEARCH DEPARTMENT
CIBA PHARMACEUTICAL PRODUCTS INC.
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(4) Tracerlab, Inc., 130 High Street, Boston 10, Mass.
(5a) British Patent 460,528; 514,411.
(5b) S. R. Aspinall, *J. Am. Chem. Soc.*, **61**, 3195 (1939).

Identification of Esculetin in Tobacco and in Cigarette Smoke

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Received January 28, 1959

In the purification of scopoletin (6-methoxy, 7-hydroxycoumarin) from cigarette smoke and from various tobacco extracts,[1,2] two or more interfering blue fluorescing compounds persisted with the scopoletin through several paper chromatographic developments. The present paper reports our identification of one of these interfering compounds as esculetin (6,7-dihydroxycoumarin).

We have identified esculetin for the first time in the leaves and flowers of oven-dried, greenhouse-grown, One-Sucker tobacco, in the tobacco of representative U. S. cigarettes, and in flue-cured and air-cured tobacco leaf samples. The mainstream smoke from representative U. S. cigarettes was found to contain esculetin in a trace amount.

The esculetin is extremely difficult to separate completely from scopoletin with such solvent systems as 15% acetic acid-water, 60% acetic acid-water; *n*-butyl alcohol–acetic acid–water (6:1:2 v./v.), and *n*-butyl alcohol–benzene-pyridine-water (5:1:3:3 v./v.), but separation on paper chromatograms may be accomplished with the solvent system nitromethane-benzene-water (2:3:5 v./v.).

In addition to its persistence with scopoletin on many paper chromatograms of various tobacco samples, esculetin may be confused on some of these chromatograms with caffeic acid. The R_f values of esculetin and caffeic acid are quite close in a number of solvent systems (Table I), and there is similarity in the bluish white fluorescence of esculetin and of caffeic acid when either is present only in low concentration on the chromatogram. Esculetin, however, behaves differently than does caffeic acid on paper chromatograms still wet with the solvent system *n*-butyl alcohol–benzene-pyridine-water. Under these conditions, esculetin fluoresces a bluish yellow when examined under long wave-length ultraviolet light (3660 Å) whereas the same concentration of caffeic acid exhibits only an extremely weak—practically imperceptible—fluorescence under the same conditions.

EXPERIMENTAL

Esculetin from tobacco flowers. Oven-dried flowers from One-Sucker tobacco plants, *Nicotiana tabacum*, grown in the greenhouse at Argonne National Laboratory, Lemont, Ill., appeared to be richer in esculetin than the leaves and other tobacco samples examined, and were, therefore, used for

(1) C. H. Yang, Y. Nakagawa, and S. H. Wender, *J. Org. Chem.*, **23**, 204 (1958).
(2) C. H. Yang, Y. Nakagawa, and S. H. Wender, *Anal. Chem.*, **30**, 2041 (1958).

many of the early identification studies on esculetin. In a typical experiment, 100 g. of tobacco flowers were extracted in a Soxhlet extractor with two 500-ml. portions of 85% isopropyl alcohol. The combined extracts were concentrated to about 100 ml. *in vacuo*, filtered, and the filtrate acidified to *p*H 2. The filtrate was then subjected to silicic acid column chromatography by a procedure adapted from that of Sondheimer[3] and based on a method described by Bulen *et al.*[4] Fifty-three grams of silicic acid (Mallinckrodt No. 2847) were mixed with the filtrate to produce a thick pasty mixture. This was made into a slurry by addition of 300 ml. of 5% *n*-butyl alcohol–chloroform saturated with 0.5*N* sulfuric acid. The slurry was poured onto silicic acid in a chromatographic column which had been prepared by thorough mixing of 160 g. of silicic acid with 110 ml. of 0.5*N* sulfuric acid, and then adding 1 l. of 5% *n*-butyl alcohol–chloroform saturated with 0.5*N* sulfuric acid. After addition of the slurry to the silicic acid in the column, the 5% *n*-butyl alcohol–chloroform system was used for packing the column. Then for developing and eluting the components of the tobacco flowers, 5%, 15%, 25%, 35%, and 50% *n*-butyl alcohol–chloroform systems saturated with 0.5*N* sulfuric acid were used. Eluate fractions of 500 ml. were collected, concentrated to 100 ml. *in vacuo*, and studied by paper chromatography. The second 500-ml. fraction eluted from the column with the 5% *n*-butyl alcohol system contained the major portion of the esculetin present in the tobacco flowers. This second fraction, after concentration *in vacuo*, was subjected to mass paper chromatography for purification of the esculetin. This eluate was streaked onto four sheets of S & S No. 589, red ribbon, chromatography paper, size 58 × 58 cm., and developed in ethyl acetate–formic acid–water (10:2:3 v./v., upper layer). The bluish white fluorescing zone (approximate R_f = 0.76), containing the esculetin and impurities, was cut out and sewn onto new sheets of the S & S chromatography paper. These were developed in 15% acetic acid–water until the esculetin moved across the bottom thread line. The sheets were then removed from the chamber, dried, and developed in the nitromethane-benzene-water system. The esculetin zone on each paper was cut out, sewn onto still other sheets of the chromatography paper, and developed again in the ethyl acetate–formic acid–water system. The bluish white fluorescing zone, R_f = 0.76, was cut out from each sheet and eluted with 95% ethyl alcohol. The combined alcohol elutions were then studied for proof of identity of esculetin.

The eluted esculetin separated from the tobacco flowers extract was co-chromatographed with the authentic reference esculetin in all the solvent systems mentioned in this paper, both on one- and two-dimensional chromatograms. Typical R_f values are reported in Table I. The eluted esculetin also exhibited the same colors and fluorescence as produced by the authentic reference esculetin when treated with chromogenic sprays (Table II). The phosphotungstic acid and the 10% ammonium hydroxide spray reagents were used in detecting 1-, 2-, and 1,4-hydroxyphenols by Hermann.[5]

TABLE I

R_f VALUES OF ESCULETIN, SCOPOLETIN, AND CAFFEIC ACID

Compound	Solvent Systems[a]					
	(1)	(2)	(3)	(4)	(5)	(6)
Esculetin	0.84	0.84	0.78	0.83	0.09	0.47
Caffeic acid	0.81	0.85	0.80	0.84	0.03	0.42[b]
Scopoletin	0.84	0.82	0.83	0.89	0.80	0.50

[a] Solvent systems: (1) *n*-butyl alcohol–benzene-pyridine-water (5:1:3:3 v./v., upper layer); (2) isopropyl alcohol–pyridine–acetic acid–water (8:8:1:2 v./v.); (3) *n*-butyl alcohol–acetic acid–water (6:1:2 v./v.); (4) ethyl acetate–95% formic acid–water (10:2:3 v./v.); (5) nitromethane-benzene-water (2:3:5 v./v., upper layer); (6) 15% acetic acid–water. [b] A minor spot (R_f = 0.50) was also present.

TABLE II

COLOR[a] REACTIONS OF ESCULETIN, CAFFEIC ACID, AND SCOPOLETIN

Spray Reagent	Compound		
	Esculetin	Caffeic acid	Scopoletin
None, U.V.	Bl-w	bt-Bl	bt-d-Bl
NH_3 vapor, U.V.	bt-Y-Bl	bt-Bl-(e)	bt-Bl
10% NH_4OH and NH_3 vapor, U.V.	bt-Bl-G	bt-Bl	bt-d-Bl
1% alc. $AlCl_3$, U.V.	bt-lt-Bl	bt-Bl	bt-d-Bl
1% alc. $AlCl_3$, NH_3, U.V.	Bl-Y	Bl-W-Y	bt-d-Bl
Phosphotungstic acid and alc. KOH, U.V.	bt-Y	bt-Y	bt-Bl
Phosphotungstic acid and alc. KOH, V.	ft-Y	ft-Y	N
0.5% $KMnO_4$, aq. V.	N	bt-Y → Br	N
Diazotized *p*-nitroaniline and Na_2CO_3, V.	N	Y → Br	N

[a] V = visible light, U.V. = ultraviolet light, Bl = blue, Br = brown, G = green, W = white, Y = yellow, bt = bright, d = deep, (e) = enhanced, ft = faint, lt = light, N = no color, → = changing to.

The ultraviolet absorption spectrum of the reference esculetin in 50% ethyl alcohol–water, as determined on a Beckman spectrophotometer, Model DU, exhibited major maxima at 228 and 328 mμ, and a major minimum at 274 mμ. Minor maxima occurred at 254 and 299 mμ, and minor minima at 222, 249, and 310 mμ. The eluted esculetin separated from tobacco flowers gave an identical spectrum, using as a blank a 50% ethyl alcohol–water eluate from the S & S filter paper. The absorption curves of the separated esculetin and the reference esculetin check with the literature.[6]

Preparation of the reference esculetin. Esculetin was prepared from its commercially available glycoside esculin (esculetin-6-glucoside). Ten g. of esculin (Nutritional Biochemical Corp., Cleveland, Ohio) were suspended in 350 ml. of 7% sulfuric acid and heated on a steam bath for 6 hr. The hydrolysate was filtered hot. The fine, needle-like crystals were washed with water and then with ether. The filtrate was cooled overnight. Additional crystals separated and were washed as above. The precipitates were combined, and then the crude esculetin, after decolorization with charcoal, was recrystallized from 95% ethyl alcohol. All commercial samples of esculin that were examined by paper chromatography were found to contain blue fluorescent impurities, and even after hydrolysis and crystallization, the resulting esculetin (4.1 g.) was still not chromatographically pure. Therefore, purification was undertaken by column chromatography of the crystalline esculetin. Two g. were dissolved in methyl alcohol and applied to a column packed with pre-washed Magnesol (Food Machinery and Chemical Corp., N. Y.). The column was developed with ethyl acetate saturated with water. The first 250 ml. of eluate contained impurities and were not used. The subsequent eluates were combined and concentrated *in vacuo*. The resulting precipitate was recrystallized from 95% ethyl alcohol and then sublimed *in vacuo*. This chromato-

(3) E. Sondheimer, *Arch. Biochem. & Biophys.*, **74**, 131 (1958).

(4) W. A. Bulen, J. W. Varner, and R. C. Burrell, *Anal. Chem.*, **24**, 187 (1952).

(5) K. Hermann, *Pharm. Zentralhalle*, **95**, 56 (1956).

(6) R. H. Goodwin and B. M. Pollock, *Arch. Biochem. & Biophys.*, **49**, 1 (1954).

graphically pure esculetin (300 mg.) was used as the reference esculetin, m.p. 270°, with decomposition.[7]

Esculetin in tobacco leaves and in cigarette tobacco. For identification of the relatively smaller amount of esculetin present in tobacco leaves, the procedure described above for tobacco flowers was used. In addition, for some samples, a paper chromatographic procedure was employed which did not involve the preliminary silicic acid chromatography. The first steps of this procedure were the same through the development with the nitromethane-benzene-water system as those already described by Yang *et al.*[2] for the quantitative determination of scopoletin in cigarette tobacco. With the nitromethane system, the scopoletin (R_f = 0.84) moved far ahead of the esculetin (R_f = 0.07). This time, the esculetin zone, still containing another interfering blue fluorescent compound, was cut out and eluted with methyl alcohol. The eluates were streaked on new sheets of S & S paper and developed in 15% acetic acid–water, and then again in the nitromethane system. Each section containing the esculetin was cut out, sewn on a new sheet, developed in the ethyl acetate–formic acid–water system to move the esculetin across the sewing line, and the paper removed and dried. The unfinished chromatogram was then developed again in 15% acetic acid–water to effect the separation of esculetin from the other blue fluorescent compound. Usually esculetin moved sufficiently ahead of the interfering substance at this point to be eluted with methyl alcohol as a chromatographically pure compound and then be identified beyond doubt as esculetin. If not completely separated, the esculetin zone was placed on yet another paper and rechromatographed in the 15% acetic acid–water before making further identification studies.

By one or both of the above procedures, esculetin was identified as being present in a small amount in leaves of Burley tobacco (Kentucky 16), Turkish tobacco (imported and domestic), and flue-cured tobacco (Hicks) from North Carolina.

Because of the low amount of esculetin present relative to that of scopoletin in cigarette tobacco, 8 g. samples were used for these analyses instead of the 2 g. samples used for analysis of scopoletin. Also, Whatman No. 3 MM chromatography paper was used for the first step only in the paper chromatography. The S & S No. 589 red ribbon paper was used for the other paper chromatographic steps. Cigarettes analyzed included Camel, Lucky Strike, Philip Morris, Old Gold Straights, Pall Mall, Viceroy, Winston, and Oasis.

Esculetin in the mainstream smoke from cigarettes. The sampling and smoking of 8 brands of cigarettes for esculetin analysis were similar to those already described for scopoletin by Yang *et al.*[2] The separation, purification, and identification of esculetin from the cigarette smoke condensates were carried out by mass paper chromatography in the same manner described above for esculetin in tobacco leaves. Because esculetin was present only in trace amounts in the smoke, eluates representing smoke from 4 packs of cigarettes had to be combined and concentrated to obtain sufficient esculetin for unambiguous chromatographic studies.

Acknowledgment. This work and some previous research on which these findings are based were supported in part by the Tobacco Industry Research Committee and by the Atomic Energy Commission.

We also sincerely thank Dr. Norbert Scully and Mr. Will Chorney of the Argonne National Laboratory, Dr. C. W. Nystrom, R. J. Reynolds Tobacco Co., Dr. J. M. Moseley, American Tobacco Co., and Luther Shaw, Waynesville, N. C., for supplying various tobacco fractions used.

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(7) Handbook of Chemistry and Physics, 38th ed., Chemical Rubber Publishing Co., Cleveland, Ohio, 1956.

Addition of Dinitrogen Pentoxide to Stilbene

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Received January 29, 1959

The reaction of dinitrogen pentoxide and simple olefins to produce 1,2-nitronitrates has been shown to be a *cis* addition process.[1] As part of this study the reaction of dinitrogen pentoxide and *cis*- and *trans*-stilbene has been investigated. Recently, the *cis* addition of acetyl nitrate to *trans*-stilbene was reported and DL-*threo*-α-acetoxy-α′-nitrobibenzyl was characterized.[2] This compound was a key intermediate in the proof of configuration of the expected products of the dinitrogen pentoxide-stilbene reaction, the α-nitrato-α′-nitrobibenzyls.

Addition of dinitrogen pentoxide to *trans*-stilbene in the presence of tetraethylammonium nitrate[1] produced a mixture of α-nitrato-α′-nitrobibenzyls (81% yield) which was separated into compounds melting at 96° and 165°. The 96° isomer was the predominant product; quantitative infrared analysis of the mixture isolated indicated that it comprised at least 81% of this mixture. Assignment of the *threo* configuration to this α-nitrato-α′-nitrobibenzyl, m.p. 96°, was made on the basis that the same α-hydroxy-α′-nitrobibenzyl[3] which produced the DL-*threo*-α-acetoxy-α′-nitrobibenzyl, m.p. 135°,[2] was converted to the nitronitrate of m.p. 96° on nitration with dinitrogen pentoxide. Thus, the addition of dinitrogen pentoxide to *trans*-stilbene was predominantly a *cis* process.

When the addition of dinitrogen pentoxide to *cis*-stilbene was attempted under the conditions of the *trans*-stilbene addition little reaction occurred and most of the stilbene was recovered.[4] Increasing the reaction time led to a higher yield of nitrated products, but considerable ring nitration apparently occurred. However, the DL-*erythro*-α-nitrato-α′-nitrobibenzyl, isolated in 8.6% yield, comprised a

(1) T. E. Stevens and W. D. Emmons, *J. Am. Chem. Soc.*, 79, 6008 (1957).

(2) G. Drefahl and H. Crahmer, *Ber.*, 91, 745 (1958).

(3) The *threo*-α-hydroxy-α-nitrobibenzyl, m.p. 106°, was obtained from the stilbene–dinitrogen tetroxide reaction, the details of which will be reported later. DL-*Erythro*-α-hydroxy-α′-nitrobibenzyl, m.p. 99°, also was obtained from this reaction and was converted to DL-*erythro*-α-acetoxy-α′-nitrobibenzyl, m.p. 116°.

(4) The recovered stilbene was mainly the *trans* form, but isomerization undoubtedly took place during the work-up of the reaction mixture. In the reaction of acetyl nitrate and *cis*-stilbene isomerization proceeded faster than addition.[2]

larger percentage of the nitronitrate fraction than it did in the *trans*-stilbene experiment, indicating that the *cis* addition process, though slow, was operative.

EXPERIMENTAL[5]

Reaction of trans-stilbene and dinitrogen pentoxide. A stirred solution of 3.0 g. (16.6 mmoles.) of stilbene and 3.5 g. (18 mmoles.) of tetraethylammonium nitrate in 100 ml. of methylene chloride was cooled to −20° while 16.6 mmoles. of dinitrogen pentoxide in 18.5 ml. of methylene chloride was added over 15 min. After addition of the dinitrogen pentoxide the mixture was stirred at −5° for 15 min. and at 3° for 45 min. Water (100 ml.) was then added to the reaction mixture and the organic layer was separated and washed with aqueous sodium bicarbonate and water and dried over magnesium sulfate. Removal of the methylene chloride left 4.0 g. of residue. The residue was taken up in methylene chloride and chromatographed on a 2.8 × 40 cm. silica gel column. Elution of the column with ligroin–methylene chloride 1:1 gave a fraction which after trituration with ligroin consisted of 3.84 g. (81%) of mixed *threo*- and *erythro*-α-nitrato-α′-nitrobibenzyls, m.p. 74–78°. A 2.00-g. portion of this mixture was recrystallized from ligroin four times to give *erythro*-α-nitrato-α′-nitrobibenzyl, 0.07 g., m.p. 157–160°. Further recrystallization from ligroin raised the m.p. to 165–166° dec.

Anal. Calcd. for $C_{14}H_{12}N_2O_5$: C, 58.33; H, 4.20; N, 9.72. Found: C, 58.80; H, 4.24; N, 9.28.

The ligroin filtrate[6] on standing deposited *threo*-α-nitrato-α′-nitrobibenzyl as a cluster of needles, m.p. 95.5–96.5°. Three recrystallizations from ligroin gave long needles, m.p. 96–97°.

Anal. Calcd. for $C_{14}H_{12}N_2O_5$: C, 58.33; H, 4.20; N, 9.72. Found: C, 58.67; H, 4.77; N, 9.65.

The amount of *threo* isomer present in the mixture isolated was determined by quantitative infrared analysis using dimethyl sulfoxide as solvent and the 11.37 μ band present only in the *threo* compound as a reference. The sample was found to be 81% the *threo* isomer; the remainder was assumed to be the *erythro*-nitronitrate.

Reaction of cis-stilbene and dinitrogen pentoxide. The procedure outlined above for the nitration of *trans*-stilbene was followed using 3.0 g. of *cis*-stilbene. The nitronitrate fraction isolated after chromatography weighed 0.51 g. When the nitration was allowed to proceed for 2 hr. at 3° and the residue handled as usual, there was obtained from the chromatographic column *trans*-stilbene, 0.88 g. (29%), identified by m.p. and infrared spectrum and a nitronitrate fraction of 1.13 g. Two recrystallizations of this material from ligroin gave DL-*erythro*-α-nitrato-α′-nitrobibenzyl, 0.41 g., 8.6%, m.p. 159–162°.

Nitration of threo-α-hydroxy-α′-nitrobibenzyl. A stirred solution of 0.78 g. (3.2 mmoles.) of *threo*-α-hydroxy-α′-nitrobibenzyl and 2.0 g. of tetraethylammonium nitrate in 50 ml. of methylene chloride was cooled to −20° while 3.6 mmoles. of dinitrogen pentoxide in 4 ml. of methylene chloride was added dropwise. After addition of the dinitrogen pentoxide the solution was allowed to warm to 0° over 1 hr. The organic layer was then washed with water, aqueous sodium bicarbonate, and water, and was dried over magnesium sulfate. The methylene chloride solution was concentrated to 25 ml. and then chromatographed on a 2.5 × 12 cm. silica gel column. The material eluted by 150 ml. of methylene chloride, 0.89 g. (97%), m.p. 87–93° was found to be 100% *threo*-α-nitrato-α′-nitrobibenzyl by analysis of its infrared spectrum. One recrystallization from ligroin gave needles, m.p. 96–97°.

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(5) All melting points are uncorrected.

(6) Except on this one occasion when the *threo*-nitronitrate crystallized in a clump and was separated mechanically, the *threo* compound could not be purified by recrystallization. Crystals melting at 85–96°, about 90% pure by infrared analysis, were always obtained.

Synthesis of DL-β-(5-Cytosinyl)alanine[1]

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Received February 2, 1959

With the exception of glycine, natural α-amino acids may be looked upon as β-substituted alanines. In a search for antimetabolites with possible activity against cancer, it seemed desirable to undertake the synthesis of unnatural α-amino acids in which the radical R of the formula, R—CH_2—$CH(NH_2)COOH$, would be a pyrimidine, purine, or substitution products thereof. This view was further supported by the fact that a review of the literature revealed no examples of compounds of such comparatively simple structures.

After a number of experiments using conventional methods for preparing various compounds of these types proved abortive in our hands, the procedures described below were tried and led to the successful synthesis of the first compound of this type, DL-β-(4-amino-2-hydroxy-5-pyrimidyl)alanine.

4-Amino-5-hydroxymethyl-2-methylthiopyrimidine (I) was used as a starting point for this series of reactions. The syntheses described by Ulbricht and Price[2] for I and for 4-amino-5-bromomethyl-2-methylthiopyrimidine hydrobromide (II) were modified and improved. These authors reported isolating II as a hygroscopic, noncharacterized solid.[3] In our hands, however, it was obtained as a white crystalline solid exhibiting the chemical and physical properties expected of such a substance. When II was allowed to react with diethyl acetamidomalonate in the presence of alkoxide ion, instead of the expected 2-acetamido-2-(4-amino-2-methylthio-5-pyrimidylmethyl)malonic acid, diethyl ester (III), a cyclic compound, 6-acetamido-5,6,7,8-tetrahydro-2-methylthio-7-oxopyrido[2,3-*d*]pyrimidine-6-carboxylic acid, ethyl ester (IV), was isolated. Albertson and Archer[4] described a similar occurrence in their synthesis of ornithine

(1) Taken from a portion of the thesis submitted by B. Blank to the Temple University Graduate Council in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June 1958.

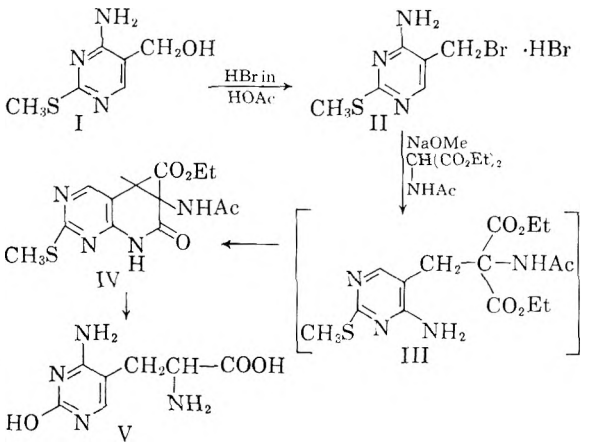
(2) T. L. V. Ulbricht and C. C. Price, *J. Org. Chem.*, **21**, 567 (1956).

(3) While this paper was being prepared, the synthesis of this compound (II) was described by T. Okuda and C. C. Price, *J. Org. Chem.*, **23**, 1738 (1958).

(4) N. F. Albertson and S. Archer, *J. Am. Chem. Soc.*, **67**, 2043 (1945).

from acrylonitrile and diethyl acetamidomalonate. In addition to elemental analysis, infrared spectral studies offered further evidence for the cyclic nature of IV as was shown by the presence of three distinct carbonyl bands at 5.7, 5.8, and 6.1 microns.

Subsequent hydrolysis of IV with concentrated hydrochloric acid followed by concentration and neutralization yielded the free amino acid, DL-β-(5-cytosinyl)alanine (V). This amino acid gave a strongly positive ninhydrin reaction. It was quite insoluble in organic solvents, but was readily soluble in dilute aqueous acids and bases. Its infrared spectra indicated the presence of a zwitterion with broad bands in the 3- and 6-micron regions. The ultraviolet spectra showed a single maximum at 283 millimicrons when determined in 0.1*N* hydrochloric acid.



EXPERIMENTAL[5]

4-Amino-5-hydroxymethyl-2-methylthiopyrimidine (I). The procedure used was a slight modification of the method described by Ulbricht and Price.[2] The use of a Soxhlet extraction apparatus was made unnecessary by the direct addition of portions of the solid 4-amino-5-carbethoxy-2-methylthiopyrimidine[2] to the stirred ethereal suspension of lithium aluminum hydride. The yields obtained from the use of this more rapid method were essentially the same as those reported.

4-Amino-5-bromomethyl-2-methylthiopyrimidine hydrobromide (II). To a saturated solution of dry hydrogen bromide in 140 ml. of anhydrous acetic acid were added, with stirring, 9.6 g. (0.06 mole) of 4-amino-5-hydroxymethyl-2-methylthiothiopyrimidine and 520 ml. of acetic acid. The slightly cloudy solution was stirred and heated on a steam bath for 2 hr. whereupon a clear solution was obtained. This solution was concentrated to a small volume in a rotary vacuum still to avoid bumping caused by the precipitation of the hydrobromide salt as the solvent was removed. The pyrimidine salt was collected on a funnel and washed with dry ether to yield 13.5 g. (76.4%) of product. This was purified by dissolving it in methanol, adding ether until the solution became cloudy, and then cooling. II was thus obtained as white needles, m.p. about 300° dec.

Anal. Calcd. for $C_6H_8BrN_3S.HBr$: C, 22.87; H, 2.88; N, 13.34. Found: C, 23.38, 23.68; H, 2.91, 3.10; N, 13.57.

6-Acetamido-5,6,7,8-tetrahydro-2-methylthio-7-oxopyrido-[2,3-d]-pyrmidine-6-carboxylic acid, ethyl ester (IV). A solution of 2.2 g. (0.04 mole) of sodium methoxide and 4.4 g. (0.02 mole) of diethyl acetamidomalonate in 25 ml. of absolute alcohol was warmed and stirred for 15 min. Then 6.3 g. (0.02 mole) of II and 50 ml. of absolute alcohol were added to the stirred solution. There was an immediate precipitation of sodium bromide. The mixture was stirred under reflux for 3 hr. and poured into three volumes of ice and water. The alcohol was removed and the aqueous solution was extracted with chloroform. The combined chloroform extracts were dried over magnesium sulfate and evaporated. The residual pale yellow oil was diluted with ether and allowed to stand overnight whereupon a yellowish white solid was obtained. This was filtered and washed with ether to yield 2.9 g. (44.6%) of product, m.p. 165–170°. Recrystallization from absolute alcohol gave white crystals, m.p. 187–188°.

Anal. Calcd. for $C_{13}H_{16}N_4O_4S$: C, 48.13; H, 4.97; N, 17.28. Found: C, 48.10, 48.06; H, 4.69, 4.79; N, 17.26, 16.97.

DL-β-(*4-amino-2-hydroxy-5-pyrimidyl*)*alanine* (V). A solution of 2.5 g. (0.007 mole) of IV in 30 ml. of concentrated hydrochloric acid was refluxed for 4 hr. The solvent was removed at reduced pressure and the white solid obtained was evaporated twice with absolute alcohol. The amino acid hydrochloride was then dissolved in water, made slightly alkaline with aqueous ammonia, cooled, and filtered to give 1.1 g. (79.8%) of product. The crude amino acid was purified by dissolving it in 10% aqueous sodium hydroxide, treating it with Celite and Norit, and filtering. The filtrate was treated with dilute hydrochloric acid and the amino acid reprecipitated. This operation was repeated and then the amino acid was dissolved in dilute hydrochloric acid and reprecipitated with concentrated aqueous ammonia at *p*H 5. Finally V was again reprecipitated from dilute base with dilute hydrochloric acid to give 400 mg. of white solid, m.p. above 300°. The analyses obtained were quite dependent upon the degree of drying. When dried at 110° *in vacuo* to constant weight, the amino acid analyzed as the monohydrate.

Anal. Calcd. for $C_7H_{10}N_4O_3.H_2O$: C, 38.88; H, 5.60; N, 25.92. Found: C, 39.47, 39.27; H, 5.86, 5.65; N, 26.20.

A picrate was prepared from the crude hydrolysis concentrate by adding a saturated solution of picric acid in water to an aqueous solution of the crude amino acid hydrochlochloride.[6] Recrystallization from water yielded the monopicrate monohydrate, m.p. 217–219° dec.

Anal. Calcd. for $C_{13}H_{13}N_7O_{10}.H_2O$: C, 35.06; H, 3.95; N, 22.01. Found: C, 35.55, 35.52; H, 3.67, 3.70; N, 21.87, 21.86.

Acknowledgment. We wish to thank the Smith Kline and French Laboratories for infrared and ultraviolet spectral data and the Temple University Council on Research and Publications for a Grant-in-Aid.

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(5) All melting points listed are uncorrected.

(6) Attempts to purify the hydrochloride by recrystallization were unsuccessful. On warming, the hydrochloride lost hydrogen chloride and was converted to the inner salt of the free amino acid (V) (the zwitterion).

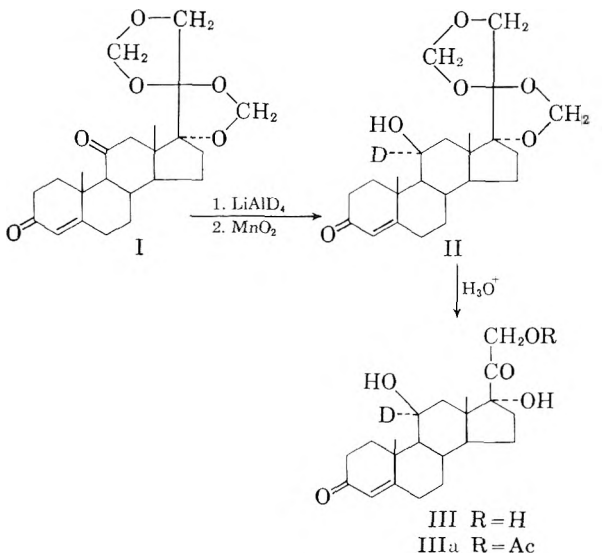
11α-Deutero-17α-hydroxy Corticosterone[1]

F. W. Bollinger and N. L. Wendler

Received February 2, 1959

The role of the 11-oxygen function in steroid metabolism has been discussed in some detail recently by Bush.[2] This author emphasizes in particular the potential significance of the reversible oxidation-reduction of the 11-oxygen function in determining pharmacological properties. In view of these considerations together with the well recognized role of the isotope effect in the oxidation of alcohols,[3] it was of interest to synthesize 11α-deuterohydrocortisone and determine its biological activity relative to hydrocortisone itself.

Cortisone in the form of its 17,20:20,21-bismethylenedioxy(BMD) derivative I[4] was reduced with lithium aluminum deuteride followed by oxidation at C-3 with manganese dioxide to give the BMD derivative of 11α-deuterohydrocortisone (II). Hydrolysis of the latter with hot 50% aqueous acetic acid according to the published method gave 11α-deutero-17α-hydroxycorticosterone (III).



In the oral glycogen deposition test in mice and in the oral systemic granuloma assay in rats, the approximate potencies relative to hydrocortisone in the two tests were 0.7–1 and 1.5, respectively.

(1) Presented at the Meeting-in-Miniature of the North Jersey Section of the American Chemical Society on January 26, 1959.

(2) I. E. Bush, *Experientia*, 12, 326 (1956).

(3) F. H. Westheimer, *Chem. Revs.*, **45**, 419 (1949).

(4) R. E. Beyler, R. M. Moriarty, F. Hoffman, and L. H. Sarett, *J. Am. Chem. Soc.*, **80**, 1517 (1958).

EXPERIMENTAL[5]

Reduction of 17,20:20,21-bismethylenedioxy-4-pregnene-3,11-dione with lithium aluminum deuteride. To a stirred solution of 3.0 g. of lithium aluminum deuteride (97% pure, 0.0693 mole) in 450 ml. of dry tetrahydrofuran under nitrogen was added a solution of 6.00 g. of 17,20:20,21-bismethylenedioxy-4-pregnene-11,20-dione in 150 ml. of tetrahydrofuran. The mixture was stirred and refluxed for 80 min. and then cooled to 5° and quenched by cautious addition of 60 ml. of ethyl acetate followed by 100 ml. of saturated sodium sulfate solution and finally 100 g. of anhydrous magnesium sulfate. The resulting mixture was filtered and the inorganic precipitate washed thoroughly with ethyl acetate. The combined filtrate and washings were taken to dryness *in vacuo* to yield 5.94 g. of product exhibiting no U.V. absorption maximum.

A solution consisting of 5.17 g. (12.7 millimoles) of the above crude reduction product was dissolved in 120 ml. of benzene and treated with 414 ml. of acetone and 62 g. of manganese dioxide. The mixture was stirred at room temperature (25°) overnight (16 hr.), filtered with the aid of Supercel, washed and the combined filtrate and washings taken to dryness *in vacuo*. The residue amounted to 4.96 g., λ_{max} 242 mμ, ϵ = 12,000. A sample crystallized from acetone-ether melted at 218–222°. Mixed m.p. with 17,20:-20,21-bismethylenedioxy-11β-hydroxy-4-pregnen-3-one was not depressed.[3]

11α-Deuterohydrocortisone 21-acetate (IIIa). To a solution of 4.94 g. of 17,20:20,21-bismethylenedioxy-11α-deutero-11β-hydroxy-4-pregnen-3-one in 245 g. of glacial acetic acid was added 245 ml. of water. The system was flushed with nitrogen and heated on the steam bath for 5.5 hr. Water was added, the mixture extracted with chloroform, the chloroform extract was extracted with bicarbonate, water, and saturated salt solution. The chloroform extract was dried over magnesium sulfate and taken to dryness *in vacuo* to yield 4.43 g. of crude 11α-deuterohydrocortisone. The latter was acetylated in 100 cc. of pyridine with 500 g. acetic anhydride at room temperature for 18 hr. The product was worked up in the usual manner and crystallized from ethyl acetate and from acetone-ether. M.p. 218–221.5°, $\lambda_{max}^{CH_3OH}$ 242 mμ, ϵ = 16,200: λ_{max}^{Nujol} 2.94, 3.02, 5.75, 5.80, 6.12 and 8.09μ.

Anal. Calcd. for $C_{23}H_{31}DO_6$: C, 68.12; H, 8.20; D, 1 atom/molecule. Found: C, 68.38; H, 8.00; D, 0.92 atom/molecule.

A solution of 1.1 g. of the 21-acetate (IIIa) in 33 cc. of methanol under reflux in a nitrogen atmosphere was hydrolyzed by addition of a solution of 1.1 g. of potassium bicarbonate in 11 cc. of water. The mixture was stirred and refluxed for 10 minutes, cooled and neutralized with acetic acid and extracted with ethyl acetate. The product was chromatographed on Florisil and eluted with (1:1) ethyl acetate-chloroform and crystallized from ethyl acetate-acetone to give 0.55 g. of *11α-deuterohydro*-cortisone (III), m.p. 217–219°, $\lambda_{max}^{CH_3OH}$ 242, ϵ = 18,000; λ_{max}^{Nujol} 2.92, 5.84, 6.07, and 6.19μ.

Anal. Calcd. for $C_{21}H_{29}DO_5$: C, 69.39; H, 8.60; D, 1 atom/molecule. Found: C, 69.47; H, 8.88; D, 0.96 atom/molecule.

A mixed m.p. of III with an authentic sample of hydrocortisone was not depressed and the flow rate of the two samples on a paper chromatogram was identical.

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(5) All melting points are corrected. The bioassays were carried out at the Merck Institute for Therapeutic Research by Dr. Silber and his collaborators.

Potential Anticancer Compounds. I. Synthesis of Thiodiacetic Acid Hydrazides and Homologs

HANS ZIMMER AND EDWARD SHAHEEN

Received February 2, 1959

The activity of bis(2-chloroethyl) sulfide and of several nitrogen analogs (nitrogen mustards) against certain types of cancer is well established.[1] However, besides a more or less pronounced toxicity, all of these compounds suffer from several unfavorable physiological properties. Therefore, the synthesis of compounds was undertaken which have the structural element $S\begin{<}^{(CH_2)_n-}_{(CH_2)_n-}$ of mustard oil but which have instead of the Cl atom the groups $-C(=O)-NHN=R$ (R = aralkylidene) or $-C(=O)-NHNHR$ (R = H or phenyl). It was hoped that these compounds would retain anticancer activity while being less toxic than the mustards. The $-C(=O)-NHN-$ group was chosen to provide the compounds with some hydrophilic solubility. Preliminary tests against three types of experimental tumors in mice, adenocarcinoma (Ca = 755), sarcoma (Sa = 180), and leukemia (L = 1210), however, showed that the compounds exhibit no activity against these tumor systems.

The compounds were prepared by established methods[2] and are compiled in Tables I and II. The corresponding bromosubstituted fatty acid es-

TABLE I

ALKYLIDENE HYDRAZIDES OF THIODIACETIC ACID AND HOMOLOGS

Compound	M.P.	Formula	C		H	
			Calcd.	Found	Calcd.	Found
		$S(CH_2CONHN=R)_2$				
R = C_6H_5CH	169–170	$C_{18}H_{18}N_4O_2S$	61.0	60.3[a]	5.1	5.2
2-ClC_6H_4CH	205–206	$C_{18}H_{16}Cl_2N_4O_2S$	51.1	50.8	3.8	3.7
4-$CH_3OC_6H_4CH$	210–212	$C_{20}H_{22}N_4O_4S$	57.9	58.1	5.3	5.6
$C_6H_5CH=CH-CH$	207–208	$C_{22}H_{22}N_4O_2S$	65.0	64.9	5.5	5.5
4-$(CH_3)_2NC_6H_4CH$	185–186	$C_{22}H_{28}N_6O_2S$	60.0	59.2[a]	6.4	6.0
2-HOC_6H_4CH	222–224	$C_{18}H_{18}N_4O_4S$	56.0	56.0	4.7	4.9
$C_6H_5CCH_3$	182–183	$C_{20}H_{22}N_4O_2S$	62.8	62.8	5.8	5.9
		$S(CH_2CH_2CONHN=R)_2$				
R = C_6H_5CH	204–206	$C_{20}H_{22}N_4O_2S$	62.8	62.6	5.8	5.8
2-ClC_6H_4CH	170–172	$C_{20}H_{20}Cl_2N_4O_2S$	53.2	53.2	4.5	4.6
4-$CH_3OC_6H_4CH$	145	$C_{22}H_{26}N_4O_4S$	59.7	59.7	5.9	5.9
$C_6H_5CH=CH-CH$	237–240	$C_{24}H_{26}N_4O_2S$	66.3	66.1	6.0	6.1
4-$(CH_3)_2NC_6H_4CH$	247–250	$C_{24}H_{32}N_6O_2S$	61.5	61.5	6.9	6.9
2-HOC_6H_4CH	236–238	$C_{20}H_{22}N_4O_4S$	58.0	58.0	5.3	5.5
$C_6H_5CCH_3$	205–207	$C_{22}H_{26}N_4O_2S$	64.4	63.4[a]	6.4	6.6
		$S(CH_2CH_2CH_2CONHN=R)_2$				
R = C_6H_5CH	130–132	$C_{22}H_{26}N_4O_2S$	64.4	63.5[a]	6.4	6.4
2-ClC_6H_4CH	172–175	$C_{22}H_{24}Cl_2N_4O_2S$	55.1	53.7[a]	5.0	4.9
4-$CH_3OC_6H_4CH$	137–138	$C_{24}H_{30}N_4O_4S$	61.2	60.2[a]	6.4	6.2
$C_6H_5CH=CH-CH$	201–203	$C_{26}H_{30}N_4O_2S$	67.5	67.2	6.5	6.4
2-HOC_6H_4CH	193–195	$C_{22}H_{26}N_4O_4S$	59.7	59.8	5.9	6.1
$C_6H_5CCH_3$	151–153	$C_{24}H_{30}N_4O_2S$	65.7	63.7[a]	6.9	6.7
		$S[CH(CH_3)CONHN=R]_2$				
R = C_6H_5CH	223–224	$C_{20}H_{22}N_4O_2S$	62.8	62.5	5.8	5.7
2-ClC_6H_4CH	243–244	$C_{20}H_{20}Cl_2N_4O_2S$	53.2	53.3	4.5	4.5
4-$CH_3OC_6H_4CH$	239–240	$C_{22}H_{26}N_4O_4S$	59.7	59.9	5.9	6.0
$C_6H_5CH=CH-CH$	231–232	$C_{24}H_{26}N_4O_2S$	66.3	66.0	6.0	6.0
4-$(CH_3)_2NC_6H_4CH$	234–235	$C_{24}H_{32}N_6O_2S$	61.5	61.4	6.9	7.1
2-HOC_6H_4CH	225–226	$C_{20}H_{22}N_4O_4S$	58.0	58.2	5.4	5.5
$C_6H_5CCH_3$	212–213	$C_{22}H_{26}N_4O_2S$	64.4	64.2	6.4	6.8

[a] The analysis could not be improved by further recrystallization.

(1) Jesse P. Greenstein, "Biochemistry of Cancer," Academic Press Inc., New York, N. Y., 1954, p. 282.

TABLE II

HYDRAZIDES OF THIODIACETIC ACID AND HOMOLOGS

Compound	M.P.	Formula	C		H	
			Calcd.	Found	Calcd.	Found
		$S(CH_2CONHNHR)_2$				
R = H	117–119[a]	$C_4H_{10}N_4O_2S$	26.9	27.2	5.6	5.6
C_6H_5	212–215	$C_{16}H_{18}N_4O_2S$	58.2	58.2	5.5	5.4
		$S(CH_2CH_2CONHNHR)_2$				
R = H	152–153	$C_6H_{14}N_4O_2S$	34.9	35.0	6.8	6.9
C_6H_5	204–206[b]	$C_{18}H_{22}N_4O_2S$	60.3	59.6	6.2	6.3
		$S(CH_2CH_2CH_2CONHNR)_2$				
R = H	*128–131*[c]	$C_8H_{18}N_4O_2S$	*41.0*	*41.0*	7.7	7.7
C_6H_5	151–153	$C_{20}H_{26}N_4O_2S$	62.1	60.6[d,e]	6.8	6.6
		$S[CH(CH_3)CONHNR]_2$				
R = H	174–175[b]	$C_6H_{14}N_4O_2S$	34.9	35.8	6.8	7.1
C_6H_5	*169–170*	$C_{18}H_{22}N_4O_2S$	60.3	62.5[e]	6.2	6.2

[a] Recrystallized from methanol. [b] Recrystallized from methanol/dimethylformanide. [c] W. Reppe, *Ann.*, **596**, 158 (1955), m.p. 130°. [d] Recrystallized from ethanol/dimethylformanide. [e] The analysis could not be improved by further recrystallization.

ters were treated with sodium sulfide in aqueous ethanol. The thiodiacid esters were isolated and, on reaction with excess hydrazine, furnished the corresponding hydrazides. The latter were converted into the aralkylidene hydrazides by the method of Zimmer and George.[3] The hydrazides are characterized by an extremely low solubility in most of the common solvents. They are, however, soluble in *N,N*-dimethylformamide and can be recrystallized from this solvent. They all have rather unsharp melting points and melt with considerable decomposition. Therefore, these derivatives are not well suited for possible identification of carbonyl compounds. In the preparation of the phenylhydrazides,[4] it was found advantageous to use the acids rather than the esters as starting materials.

EXPERIMENTAL

Melting points are uncorrected. Microanalyses are by A. Bernhardt, Microanalytisches Laboratorium im Max-Planck-Institut, Mulheim/Ruhr, Germany.

Materials. Generally, Eastman White Label products or comparable grades were employed without further purification. Ethyl 4-bromobutyrate was obtained from Fluka, A.G., Buchs, Switzerland.

The preparations of the hydrazides were generally performed as follows: To a solution of the corresponding thiodiacid diester (0.05 mole) in 25 ml. absolute methanol, a 30% excess of hydrazine hydrate (85%) was added. After 3 drops of glacial acetic acid had been added as a catalyst, the mixture was refluxed for about 3 hr. After the mixture was cooled, an additional 25 ml. of absolute methanol was added, and the mixture was left overnight for crystallization. An additional crop of compound could be obtained by keeping the mother liquor for a short period in the refrigerator. The compounds were recrystallized from a minimum amount of *N,N*-dimethylformamide (Table II).

3,3'-Thiodipropionic acid, bis(p-dimethylaminobenzylidenehydrazide). To a solution of 2.67 g. (0.015 mole) of 3,3'-thiodipropionic acid dihydrazide in 40 ml. of water, a solution of 5.97 g. (0.04 mole) of *p*-dimethylaminobenzaldehyde in 70 ml. of ethanol was added. After a brief period, crystals began depositing and were collected after about 1 hr. They were washed with ethanol and air-dried. Yield, 5.69 g. (81%), m.p. 247–250°. The analytical sample was recrystallized from *N,N*-dimethylformamide, m.p. 247–250° (dec.). The remaining aralkylidene hydrazides were prepared similarly (Table I).

3,3'-Thiodipropionic acid, bis(phenylhydrazide). To a solution of 6.5 g. phenylhydrazine in 25 ml. tetrahydrofuran, 3.56 g. (0.02 mole) of 3,3'-thiodipropionic acid was added. After being refluxed for 7 hr., the mixture was cooled and the deposited phenylhydrazide was filtered and washed with ether. Yield, 5.02 g. (70%), m.p. 197–200°. The analytical sample was recrystallized from a minimum amount of *N,N*-dimethylformamide, m.p. 204–206°. The remaining phenylhydrazides were prepared similarly (Table II).

Acknowledgment. The authors gratefully acknowledge the financial help by the National Institutes of Health through grant CY-2904. The test results were obtained by the Cancer Chemotherapy National Service Center, National Institutes of Health, Bethesda 14, Md.

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(2) G. M. Bennett and L. V. D. Scorah, *J. Chem. Soc.*, 194 (1927); J. M. Loven, *Ber.*, 29, 1136 (1896).

(3) H. Zimmer and D. K. George, *Chem. Ber.*, 89, 2285 (1956).

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A Procedure for Converting Aryl Halides to High Molecular Weight Phenols

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Received February 5, 1959

Authentic specimens of phenols were desired for part of an extensive program on characterizing

TABLE I

PREPARATION OF SOME HIGH MOLECULAR WEIGHT PHENOLS

Compound	Yield, %	M.p.	$\lambda_{max}^{cyclohexane}$, mμ	Log ε
2-Fluorenol	23	169–170[a]	315.2, 308.3, 304.0, 282.3, 276.5, 271.0, 267.0, 262.0	3.76, 3.72, 3.74, 4.18, 4.25, 4.33, 4.30, 4.22[b]
5-Acenaphthenol	15	121.5–123[c]	331, 323.5, 316.0, 301.2, 290.5	3.69, 3.55, 3.70, 3.82, 3.78[d]
2-Methyl-1-naphthol	51	61–63[e]	330.0, 324.2, 316.3, 310.0, 303.2, 296.5, 292.5, 285.0	2.97, 3.35, 3.29, 3.45, 3.52, 3.64, 3.65, 3.63
4-Methyl-1-naphthol	33	83–85[f]	326.6, 318.8, 312.2, 305.0, 299.6, 290.0	3.50, 3.51, 3.63, 3.68, 3.75, 3.67
3-Phenylphenol	61	72–74[g]	290.0, 281.0, 249.0	3.50, 3.60, 4.21[h]

[a] M.p. 171°, I. Heilbron and H. M. Bunbury, *Dictionary of Organic Compounds*, Oxford University Press, New York, 1953. [b] $\lambda_{max}^{cyclohexane}$ 315.2, 308.3, 304.0, 282.3, 276.5, 271.0, 267.0, 262.0 mμ (log ε 3.75, 3.70, 3.74, 4.17, 4.24, 4.32, 4.31, 4.26), R. A. Friedel and M. Orchin, *Ultraviolet Spectra of Aromatic Compounds*, John Wiley & Sons, New York, 1951. [c] M.p. 125–126°, H. Rapoport, T. P. King, and J. B. Lavigne, *J. Am. Chem. Soc.*, **73**, 2718 (1951). [d] Log ε values reliable only with respect to relative size since precise concentration of saturated solution used was not known. [e] M.p. 62.4°, P. P. T. Sah, *Rec. trav. chim.*, **60**, 373 (1941). [f] M.p. 84–85° (Heilbron). [g] M.p. 72–76°, G. F. Woods, F. T. Reed, T. E. Arthur, and H. Ezekial, *J. Am. Chem. Soc.*, **73**, 3854 (1951). [h] λ_{max}^{EtOH} 290, 287, 249 mμ (log ε 3.52, 3.58, 4.20), V. Prelog, O. Metzler, and O. Jeger, *Helv. chim. acta*, **30**, 675 (1947).

components isolated from low temperature coal tars. Hawthorne has presented a procedure for converting aryl halides to the corresponding phenols, in which he demonstrated good yields for phenol, 1-naphthol, and 4-methylphenol.[2] Since a relatively large number of aryl halides has been made available for purchase in recent years, this apparently general method of synthesizing phenols seemed to offer an appealingly ready route for preparing authentic specimens. However, it was soon discovered that most of the higher molecular weight aryl halides gave little or no phenol according to the procedure described by Hawthorne.

The difficulty was readily shown to lie in lack of oxidation of the arylboronic acid with 10% hydrogen peroxide. Good yields of the arylboronic acid could be obtained from the reaction of methyl borate with the arylmagnesium halide, but the subsequent oxidation to the phenol failed to take place. Kuivila[3] has demonstrated that the reaction of hydrogen peroxide with benzeneboronic acid proceeds by way of the hydroperoxide ion, HOO^-, which attacks the boron atom. The rate of the reaction depends on concentration of hydroperoxide ion, as shown by Kuivila; it is also logical to assume that an increase in reaction temperature will increase the reaction rate. Therefore 30% hydrogen peroxide was used in place of 10% hydrogen peroxide and, possibly of more importance, the original refluxing ether solution employed by Hawthorne during the oxidation step was replaced by a refluxing benzene solution. This meant an increase of about 45° in the reaction temperature. Under these conditions most of the high molecular weight arylboronic acids were readily oxidized to the corresponding phenols.

EXPERIMENTAL

Synthesis of high molecular weight phenols. A brief description of the synthesis of a few of the less common high molecular weight phenols follows.

Preparation of the Grignard reagents was straightforward, although some of the aryl halides, such as 2-bromofluorene and 5-bromoacenaphthene, were insufficiently reactive and required introduction of ethyl bromide to keep the magnesium active.[4] After the Grignard reagent was added to the ether solution of the trimethyl borate, as described by Hawthorne, the reaction mixture was refluxed 15 min. as recommended by Seaman and Johnson for increased yields of arylboronic acid.[5] Nearly all of the ether was removed by evaporation over a water bath, and an equivalent volume of benzene was added. This benzene solution was heated to reflux and 30% hydrogen peroxide was added slowly in a nitrogen atmosphere and the reaction mixture refluxed for 45 min. The remainder of the procedure was essentially that described by Hawthorne. Yields given in Table I are based on the aryl halides.

Infrared spectra of high molecular weight phenols. The infrared spectra were determined with a Perkin-Elmer Model 21 instrument, using about 1.1 to 1.5% in potassium bromide pellets for all of the phenols except 5-acenaphthenol, for which a 0.70% cyclohexane solution was used in a 0.5 mm. sodium chloride cell. The absorption bands of analytical significance are presented in Table II. These have not been reported previously in the literature.

TABLE II

ANALYTICAL INFRARED ABSORPTION BANDS[a]

2-Fluorenol	5-Acenaphthenol	2-Methyl-1-naphthol	4-Methyl-1-naphthol	3-Phenylphenol
1266 s	1178 s	909 s	816 s	882 m
930 m	1129 s	799 vs	775 m	861 m
896 m	920 m	773 m	763 vs	853 m
853 m	826 m	742 m	739 m	754 vs
824 s	808 s	738 m		694 s
762 vs	771 vs	733 m		
728 vs		648 s		

[a] Values are frequencies in $cm.^{-1}$; vs = very strong, s = strong, m = medium.

(1) Present address: Meharry Medical College, Nashville 8, Tenn.

(2) M. F. Hawthorne, *J. Org. Chem.*, **22**, 1001 (1957).

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Acknowledgment. Special thanks are due Miss Patricia A. Estep for determining the infrared spectra.

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Reactions of Long-Chain Acids with Thiolacetates

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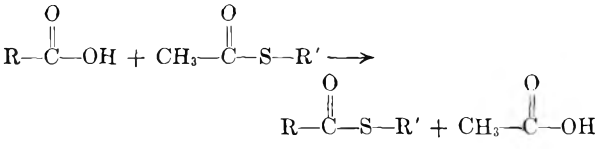
Received February 5, 1959

Vinyl esters of long-chain acids have been prepared by acidolysis of vinyl acetate in the presence of mercuric acetate and sulfuric acid.[1,2] This note describes the preparation of *n*-decyl and *n*-dodecyl thiol esters of myristic, palmitic, and stearic acids as well as *n*-dodecyl thiollaurate, *n*-butyl thiolstearate, phenyl thiolpalmitate and diphenyl dithiolsebacate by acidolysis of thiolacetates with long-chain acids in 46–61% yield. The results of these reactions are summarized in Table I. We



believe that this is the first reported instance of the acidolysis of thiol esters. Traces of unreacted acids were removed from the crude thiol esters by chromatography with Florisil.

TABLE I

THIOL ESTERS PREPARED BY ACIDOLYSIS

	M.P.	Yield, %
n-Dodecyl thiollaurate	37–38	48
n-Decyl thiolmyristate	38–38.5	61
n-Dodecyl thiolmyristate	43.5–44	46
n-Decyl thiolpalmitate	43–44	48
n-Dodecyl thiolpalmitate	48–49	51
n-Decyl thiolstearate	50–50.5	51
n-Dodecyl thiolstearate	54–55	47
Phenyl thiolpalmitate	28–28.5	60
Diphenyl dithiolsebacate	60–61	52
n-Butyl thiolstearate	31–32	49

Attempts to prepare the monophenyl thiol ester of sebacic acid by the reaction of sebacic acid and phenyl thiolacetate were unsuccessful. Heating of equimolar ratios of sebacic acid and phenyl thiolacetate in the presence of 100% sulfuric acid and mercuric acetate for 6 hr. on a steam bath resulted in the formation of diphenyl dithiolsebacate. A similar experiment with two molar ratio of sebacic acid to phenyl thiolacetate yielded diphenyl dithiolsebacate and not monophenyl thiolsebacate.

EXPERIMENTAL

Starting materials. Lauric, myristic, palmitic and stearic acids, *n*-decanethiol, *n*-dodecanethiol, *n*-butanethiol, thiophenol, and acetyl chloride were the best available commercial materials and were used as received.

n-Decyl thiolacetate. A mixture of 17.4 g. (0.1 mole) of *n*-decanethiol and 11.8 g. (0.15 mole) of acetyl chloride was allowed to stand overnight at room temperature. The reaction mixture then was heated on a steam bath for 4 hr., dissolved in 100 ml. of ether, washed with water until the washings were neutral to litmus, and the ether solution was dried over anhydrous sodium sulfate. The ether was removed by distillation and the product was distilled under diminished pressure. Yield, 16.1 g. (74.5%), b.p. 91–92° at 0.3 mm., n_D^{30} 1.4595, d_4^{30} 0.8956.

Anal. Calcd. for $C_{12}H_{24}OS$: S, 14.8. Found: S, 14.4. Molecular Refraction Calcd. 66.03. Found: 66.11.[3] *n*-Butyl thiolacetate[4] b.p. 160–163°, *n*-dodecyl thiolacetate[5] b.p. 164–166° at 10 mm. and phenyl thiolacetate[6] b.p. 110° at 12 mm. were prepared in an analogous manner.

General acidolysis reaction. To 0.05 mole of thiolacetate and 0.025 mole of the appropriate fatty acid in a 200 ml. round bottomed flask, fitted with a reflux condenser, was added 0.1 g. of mercuric acetate and one drop of 100% sulfuric acid and the reaction mixture was heated on a steam bath for 4 hr. After cooling to room temperature, 0.3 g. of sodium acetate dihydrate was added and the product was crystallized from acetone or acetone-alcohol mixture. To remove traces of unreacted acids, the thiol esters were chromatographed, using 12 g. of Florisil per gram of thiol ester. The column was eluted with a total of 400 ml. of petroleum ether and after the solvent was removed by distillation, the product was crystallized once from acetone or acetone-alcohol mixture. The thiol esters showed no depression of melting point when mixed with an authentic sample. These compounds were prepared by methods described in previous papers.[7–9]

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(1) W. J. Toussaint and L. G. MacDowell, Jr., U.S. Patent 2,299,862 (1942).

(2) D. Swern and E. F. Jordan, Jr., *J. Am. Chem. Soc.*, 70, 2334 (1948).

(3) Molecular refractions were calculated using the values reported by A. J. Vogel, *J. Chem. Soc.*, 1842 (1948).

(4) F. W. Wenzel, Jr. and E. E. Reid, *J. Am. Chem. Soc.*, 59, 1089 (1937).

(5) R. L. Frank, S. S. Drake, P. V. Smith, Jr., and C. Stevens, *J. Polymer Sci.*, 3, 50 (1948).

(6) H. Boehme and H. Schran, *Chem. Ber.*, 82, 453 (1949).

(7) G. S. Sasin, R. Sasin and N. Capron, *J. Org. Chem.*, 21, 852 (1956).

(8) R. Sasin, W. F. Ashley, J. W. Manning, Jr., A. Paolini, Jr., and G. S. Sasin, *J. Am. Oil Chem. Soc.*, 35, 192 (1958).

(9) R. Sasin, G. S. Weiss, A. E. Wilfond, and G. S. Sasin, *J. Org. Chem.*, 21, 1304 (1956).

Oxidation of Hindered Phenols. VIII. Kinetics of the Oxidation of 2,4,6-Tri-*t*-butylphenol by Benzoyl Peroxide

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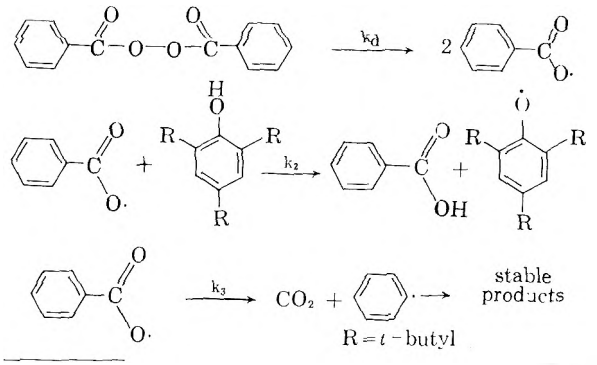
February 6, 1959

We have previously noted that the reaction of benzoyl peroxide with hindered phenols such as 2,4,6-tri-*t*-butylphenol produces the corresponding phenoxy radicals.[1] This became of particular interest in view of Walling's recent work demonstrating that most phenols (unhindered) interact with benzoyl peroxide by a relatively rapid non-radical process.[2] Walling noted that 2,4,6-tri-*t*-butylphenol was unreactive toward benzoyl peroxide at room temperature and that upon heating the characteristic blue color of 2,4,6-tri-*t*-butylphenoxy developed. He suggested that the process involves attack of benzoyloxy radicals upon the phenol and thus markedly differs from the reaction of unhindered phenols with benzoyl peroxide. Recent kinetic studies in these laboratories confirm this suggestion and provide further details on the process.

We have followed the reaction by spectophotometrically observing the rate of formation of the stable phenoxy radicals. Since these radicals have a sufficiently high molar absorbancy index (400 ± 3),[3] to make it possible to work with rather dilute solutions of the peroxide (0.005 to 0.04M), induced decomposition of the peroxide was presumably essentially eliminated.

Under these conditions, we have found that tri-*t*-butylphenol is an inefficient radical trap; to explain the kinetics of formation of tri-*t*-butylphenoxy it is necessary to assume that some of the benzoyloxy radicals are destroyed by a first order process. Since it has been observed that yields of CO_2 increase with increasing temperature,[4] we believe that this first order process is the decarboxylation of benzoyloxy radicals. Thus the process becomes:



The usual steady state kinetics applied to the above scheme (or any similar process involving the first order loss of benzoyloxy radicals) predicts that the rate of production of phenoxy radicals will be given by the expression

$$\frac{p\,(\text{Phenoxy})}{dt} = \frac{2k_dk_2\,(\text{peroxide})\,(\text{phenol})}{k_3 + k_2\,(\text{phenol})} \qquad (1)$$

This may be rearranged to yield, for the initial rate

$$\frac{(\text{phenol})_i\,(\text{peroxide})_i}{\left(\frac{d(\text{phenoxy})}{dt}\right)_i} = \frac{k_3}{2k_2k_d} + \frac{(\text{phenol})i}{2k_d} \qquad (2)$$

Equation 2 predicts that a plot of $\frac{(\text{phenol})_i\,(\text{peroxide})_i}{\left(\frac{d(\text{phenoxy})}{dt}\right)_i}$ *vs.* $(\text{phenol})_i$ should give a straight line, the slope being $^1/_2\ k_d$ and the intercept $k_3/2k_2k_d$. Figure 1 shows that this relationship does in fact provide a linear correlation of the data (summarized in Table I).

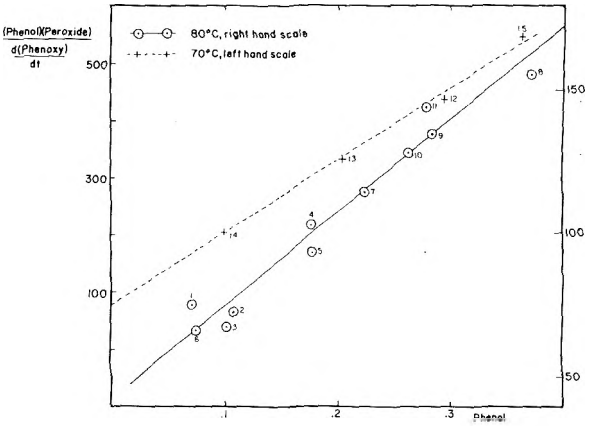


Fig. 1. Relationship of initial rate of 2,4,6-tri-*t*-butylphenoxy formation to phenol concentration in benzene solution. All concentrations in moles/l.; time in seconds

The extinction coefficient of 2,4,6-tri-*t*-butylphenoxy is sufficiently large to permit the measurement of its initial rate of formation before any appreciable consumption of peroxide or phenol has occurred. As a consequence, the value of k_d derived on this basis should agree with values for this constant derived by other measurements. The value obtained was $2.6 \pm 0.1 \times 10^{-5}$ sec.$^{-1}$ at 80°. Values derived for k_d at 80° from data cited in the literature are 2.83×10^{-5} and 2.87×10^{-5} by Hammond,[5] 4.3×10^{-5} by Swain,[6] 3.28×10^{-5} by

(1) C. D. Cook, D. A. Kuhn, and P. Fianu, *J. Am. Chem. Soc.*, **78**, 2002 (1956).

(2) C. Walling and R. B. Hodgdon, Jr., *J. Am. Chem. Soc.*, **80**, 228 (1958).

(3) C. D. Cook, C. B. Depatie, and E. S. English, unpublished work.

(4) *See Free Radicals in Solution*, C. Walling, John Wiley & Sons, Inc., New York, 1957, p. 476. See also ref. 11.

(5) G. S. Hammond, *J. Am. Chem. Soc.*, **72**, 3737 (1950). The above are Hammond's values extrapolated from 79 to 80°. One value was obtained by a normal decomposition of 0.001M peroxide solutions, the other by using iodine as a radical trap.

(6) C. G. Swain, W. Stockmeyer, and T. Clarke, Jr., *J. Am. Chem. Soc.*, **72**, 5426 (1950). This result was obtained using styrene to inhibit induced decomposition.

TABLE I

RUNS 1–11 AT 80°, RUNS 12–15 AT 70°

Run No.	Initial Peroxide Concentration Mole/l.	Peroxide Concn. at Time of Mixing Mole/l.	Initial Rate of Formation of Phenoxy Radical Moles/l./Min.	Initial Phenol Concn. Mole/l.	$\frac{(\text{Phenol})_i (\text{Peroxide})_i}{(\text{Rate of Formation of Phenoxy Radical})_i}$
1	0.0099	0.0089	8.5×10^{-6}	0.0722	75.4
2	0.0105	0.0098	14.6×10^{-6}	0.108	72.6
3	0.0099	0.0092	13.8×10^{-6}	0.101	67.4
4	0.0101	0.0095	16.4×10^{-6}	0.177	103
5	0.0101	0.0095	18.1×10^{-6}	0.177	93.4
6	0.0202	0.0188	21.0×10^{-6}	0.0738	66.1
7	0.0101	0.0095	18.5×10^{-6}	0.224	115
8	0.0085	0.0080	19.1×10^{-6}	0.371	156
9	0.0098	0.0094	19.8×10^{-6}	0.284	135
10	0.0360	0.0340	69.8×10^{-6}	0.263	128
11	0.00535	0.00490	9.5×10^{-6}	0.280	145
12	0.0200	0.0199	13.4×10^{-6}	0.296	440
13	0.0184	0.0183	11.2×10^{-6}	0.205	334
14	0.0196	0.0195	9.6×10^{-6}	0.100	208
15	0.0150	0.0149	9.9×10^{-6}	0.363	546

Bartlett,[7] 3.32×10^{-5} by Hartman,[8] and 2.01×10^{-5} by Bawn.[9]

Our value would seem to be within the accepted range. It is appreciably lower than the value of 6.5×10^{-5} sec.$^{-1}$ which Walling reports[1] for the value in the presence of 2,4,6-tri-*t*-butylphenol. However, Walling indicates that the temperature was not closely controlled and, due to the inefficiency of tri-*t*-butylphenol as a radical trap, it is likely that considerable induced decomposition occurred in the relatively concentrated solution with which he worked.

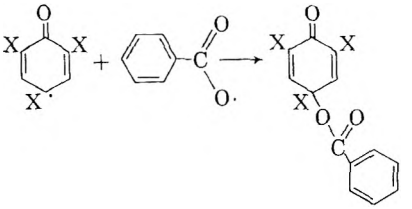
At 70° C., we obtained a value of $6.6 \pm 0.2 \times 10^{-6}$ sec.$^{-1}$ for k_d. This leads to an activation energy of 33 kcal./mole for the primary dissociation process. In view of the narrow temperature range used, we consider this in good agreement with the reported values of 29.9,[8] 29.6,[9] and 33.3.[7]

From the values of the intercepts, the ratios of k_3/k_2 are calculated to be 0.13 at 80° and 0.06 at 70°. This represents a difference in activation energy between reactions 3 and 2 of approximately 18 kcal./mole. Since hydrogen abstractions of this type are expected to have low activation energies,[10] perhaps on the order of 0–5 kcal./mole, this suggests that the activation energy for the decarboxylation of benzoyloxy radicals lies roughly in the range of 18–23 kcal./mole. In view of the uncertainties in evaluating k_3/k_2 it should be realized that no great precision can be attached to this range.

Support for the view that the competitive reaction is indeed decarboxylation comes from the fact that yields of carbon dioxide have been found to increase with increasing temperature and that both Walling[1] and we have noted relatively high yields of benzoic acid when benzoyl peroxide is decomposed in the presence of tri-*t*-butylphenol. Thus, in a typical experiment, when 0.01 mole of benzoyl peroxide in 100 ml. of benzene was heated at 80° for 48 hr., 0.0027 mole of benzoic acid was produced; when 0.01 mole of tri-*t*-butylphenol was added to such a run, 0.0094 mole of benzoic acid was produced.

These results are consistent with the work of Barson and Bevington,[11] who, by use of tracer techniques, have shown that appreciable decarboxylation of benzoyloxy radicals occurs at 60° in benzene even in the presence of such radical traps as styrene, cumene, or diphenylpicrylhydrazyl.

The fact that 2,4,6-tri-*t*-butylphenoxy can be produced in appreciable concentration in the presence of benzoyloxy radicals is in itself of considerable interest. A reaction of the type indicated by



(3)

Equation 3 would seem rather likely. However, the formation of appreciable concentrations of the phenoxy radical shows that this reaction must be relatively slow, if, indeed, it does occur. The de-

(7) K. Nozaki and P. D. Bartlett, *J. Am. Chem. Soc.*, 68, 1686 (1946).

(8) P. F. Hartman, H. G. Sellers, and D. Turnbull, *J. Am. Chem. Soc.*, 69, 2416 (1947). Calculated from data for 0.05*M* peroxide solutions.

(9) C. E. H. Bawn and S. F. Mellish, *Trans. Fara. Soc.*, 47, 1216 (1951). The above represents Bawn's data extrapolated from 76° to 80°.

(10) See A. F. Bickel and E. C. Kooyman, *J. Chem. Soc.*, 2415 (1957).

(11) C. A. Barson and J. C. Bevington, *J. Polymer Chem.*, 20, 133 (1956), see also *Tetrahedron*, 4, 147 (1958).

crease in rate of production of phenoxy radical over the first hour or so can be completely accounted for by the decrease in peroxide concentration, again implying that the above reaction is not important in our work. The fact that most of the radical has disappeared after 24 hr. at 80°, however, does suggest that this reaction, or a similar one, becomes of some importance in later stages of the reaction since disproportionation of tri-*t*-butylphenoxy is rather slow in dilute solution. Unfortunately, the reaction mixture was an intractable, oily mixture which we were unable to resolve into any pure components other than benzoic acid. It should be pointed out that since the rates are extrapolated to zero time, the incursion of the above reaction, (and also disproportionation of the phenoxy radical) should not introduce any appreciable error with the kinetic analysis.

EXPERIMENTAL

Kinetic runs. The rate of production of phenoxy radicals was followed by use of the reaction vessel shown in Fig. 2. An appropriate amount of 2,4,6-tri-*t*-butyl phenol[11] was

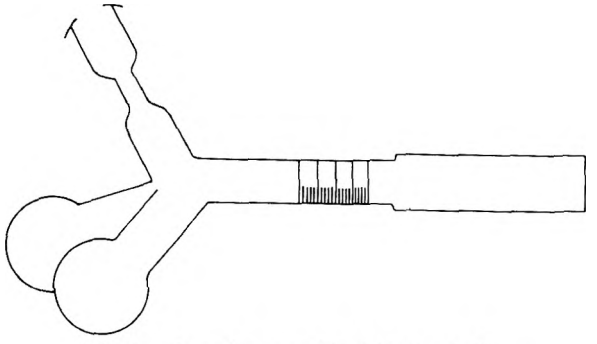


Fig. 2. Reaction vessel for kinetic studies

placed in one bulb and a solution of benzoyl peroxide in benzene introduced into the other. The vessel was then attached to a manifold by means of the ball joint and the benzene solution degassed by alternate freezing and thawing under vacuum. The vessel was sealed off at the constriction and placed in a constant temperature bath. During these operations, extreme care was taken to prevent mixing of the materials in the two bulbs. Approximately 20 min. were allowed for equilibration. The phenol was then mixed with the benzoyl peroxide solution by vigorous shaking and the apparatus placed in a Beckman DK-1 spectrometer equipped with a thermostated cabinet mounted over the cell housing. Simultaneously, the chart drive was started. The absorbancy was followed at 625 mμ for 15 to 60 min. and the initial slope, as determined with a straight-edge, was taken as $[d(\text{phenoxy})/dt]_i$. The volume was measured by means of the calibrated tube and the concentration of benzoyl peroxide at the time of mixing was calculated from this value and the time of immersion in the bath using Bartlett's equation.[5] It will be noted from Table I that these corrections were not very large.

Acknowledgment. We are indebted to the National Science Foundation for a generous grant supporting this work. Several lively discussions with Dr. Harry Blanchard were of considerable help during the execution of this work.

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(11) C. D. Cook and R. C. Woodworth, *J. Am. Chem. Soc.*, **75**, 6242 (1953).

Styrene-*p*-carboxylic Acid[1]

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Received November 24, 1958

Styrene-*p*-carboxylic acid was first prepared by Marvel and Overberger in 1945.[2] Their method involved the dehydration of *p*-(α-hydroxyethyl) benzonitrile followed by base hydrolysis of the nitrile. The carbinol was prepared from *p*-bromoacetophenone, a relatively expensive starting material.[3] The over-all yield for the four-step synthesis was 13%. A second synthesis, starting from *p*-ethylacetophenone, was reported later by Emerson *et al.*[4] It involves five steps and results in 19% over-all yields. The low yield step in each case was a potassium bisulfate dehydration.[5]

We wish to report a four-step synthesis of styrene-*p*-carboxylic acid from readily available ethylbenzene, which affords over-all yields of 24%. *p*-Bromoethylbenzene was prepared in 87% yield by the iodine-catalyzed bromination of ethylbenzene at 0° in the absence of a solvent. Treatment of this material with cuprous cyanide in pyridine afforded a 63% yield of *p*-ethylbenzonitrile, which was again brominated, this time in the α position. Treatment of the *p*-(α-bromoethyl)benzonitrile thus obtained with alcoholic potassium hydroxide resulted in simultaneous hydrolysis and dehydrobromination to yield styrene-*p*-carboxylic acid. The yields on the last two steps were 84 and 52%, respectively.

p-Bromoethylbenzene has been prepared previously by several methods.[6-9] We believe the iodine

(1) This work was performed under the auspices of the U. S. Atomic Energy Commission.

(2) C. S. Marvel and C. G. Overberger, *J. Am. Chem. Soc.*, **67**, 2250 (1945).

(3) An alternate synthesis from *p*-dibromobenzene resulted in much lower yields.

(4) W. S. Emerson, J. W. Heyd, V. E. Lucas, E. C. Chapin, G. R. Owens, and R. W. Shortridge, *J. Am. Chem. Soc.*, **68**, 674 (1946); British Patent 636,196.

(5) An alternate to dehydration, pyrolysis of *p*-cyano-α-methyl-benzylacetate, was reported by C. G. Overberger and R. E. Allen, *J. Am. Chem. Soc.*, **68**, 722 (1946). This route affords a five-step synthesis from *p*-bromoacetophenone with over-all yields of 29%.

(6) R. Fittig and J. Konig, *Ann.*, **144**, 277 (1867).

(7) P. Karrer, E. Schlitter, K. Pfaehler, and F. Benz, *Helv. Chim. Acta*, **17**, 1516 (1934).

(8) J. W. Copenhaver, M. F. Roy, and C. S. Marvel, *J. Am. Chem. Soc.*, **57**, 1311 (1935).

(9) P. S. Varma, V. Sahay, and B. R. Subramonium, *J. Indian Chem. Soc.*, **14**, 157 (1937).

catalyzed bromination presented here to be superior to any of these methods from the point of view of yield, cost, and convenience.[10]

p-Ethylbenzonitrile has been prepared from *p*-bromoethylbenzene by Dornow, Kühlcke, and Baxman[11]; but the conditions used were drastic, and the yields were low (25%). We have found a modification of the procedure of Newman[12] for α-naphthonitrile to be much more satisfactory. *p*-Ethylbenzonitrile is brominated readily in the α-position in refluxing carbon tetrachloride solution under the influence of sunlight or artificially produced ultraviolet light. The bromo compound is a colorless, viscous liquid of low volatility. It is a vesicant, causing a burning sensation on the skin, and a lacrimator. It can be distilled, but if heating is prolonged, it tends to lose hydrogen bromide and form polymers.

EXPERIMENTAL[13]

p-Bromoethylbenzene. To a stirred solution of 20 g. (0.08 mole) of iodine in 204.0 g. (1.92 mole) of ethylbenzene at 0° was added 320.0 g. (2.00 mole) of bromine. When all the bromine had been added and hydrogen bromide liberation had nearly ceased, stirring was stopped, and the reaction mixture allowed to warm to room temperature and stored overnight. After washing with 200 ml. of 10% aqueous potassium hydroxide, 100 ml. of 10% aqueous sodium bisulfite, 100 ml. of 10% potassium hydroxide and twice with 100 ml. portions of water, the reaction mixture was dried over anhydrous sodium sulfate, filtered and distilled to yield, after a small forerun, 308.0 g. (87%) of colorless bromo compound. A small amount of *p*-bromoacetophenone was removed by refraction on a 90-cm. spinning-band column at a reflux ratio of 30 to 1; b.p. 76–78°/13 mm., $d_{24.5}$ 1.343, n_D^{25} 1.5428 (*p*-bromoethylbenzene n_D^{25} 1.54228, *o*-bromoethylbenzene n_D^{25} 1.54632).[14]

p-Ethylbenzonitrile. A mixture of 59.2 g. (0.32 mole) of *p*-bromoethylbenzene, 35.0 g. (0.39 mole) of cuprous cyanide and 30 ml. of barium oxide-dried pyridine was heated under reflux for 24 hr. The resulting dark brown solution was worked up according to the *Organic Synthesis* procedure.[12] Distillation at 8 mm. gave a forerun of 1.1 ml. boiling at 74–83°/8 mm. and 26.3 g (63%) of *p*-ethylbenzonitrile b.p. 83–86°/8 mm., $n_D^{25.3}$ 1.5231, $d_{23.5}$ 0.960 (reported b.p. 103–104°/12 mm.,[11] n_D^{20} 1.5274,[15] d_{20} 0.9716[16]).

p-(α-Bromoethyl)benzonitrile. To a refluxing solution of 19.3 g. (0.15 mole) of p-ethylbenzonitrile in 100 ml. of carbon tetrachloride was added over a period of 75 min. a solution of 23.6 g. (0.15 mole) of bromine in 50 ml. of carbon tetrachloride. The reaction mixture was stirred during the addition and was irradiated with a 360-watt Uviarc fitted with an aluminum reflector.[16] After refluxing for 4 hr., the carbon tetrachloride was removed by distillation at atmospheric pressure, and the residue was distilled under reduced pressure to yield 25.8 g. (83.5%) of p-(α-bromoethyl)benzonitrile b.p. 109–111/2 mm., $d_{23.5}$ 1.375, $n_D^{25.2}$ 1.57874.

Styrene-p-carboxylic acid. p-(α-bromoethyl)benzonitrile (7.13 g., 0.034 mole) was added to a refluxing solution of 8.0 g. (0.14 mole) of potassium hydroxide and 50 mg. of hydroquinone in 35 ml. of ethanol. The mixture was heated under reflux for 48 hr., cooled to 0°, and filtered. The solid residue was dissolved in 50 ml. of water. After filtering to remove any amide or polymer, the solution was acidified with concentrated hydrochloric acid. The acid which crystallized on cooling was removed by centrifugation, washed with water, dissolved in a small amount of dilute aqueous ammonia, and reprecipitated by addition of concentrated hydrochloric acid. The precipitated acid was removed, washed with water, and dried at room temperature and 30μ pressure for 4 hr.; weight 2.62 g. (52.2%). The analytical sample was recrystallized from aqueous ethanol and sublimed at 10μ pressure and about 100°.

Anal. Calcd.: C, 72.96; H, 5.44. Found: C, 72.63; H, 5.26.

The melting point of 123–128° was not improved by further recrystallization. Marvel and Overberger[2] report 143–144° for material presumably free of ortho isomer.

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(10) Judging from index-of-refraction measurements, about 12.5% orthoisomer is produced. A small amount of *p*-bromoacetophenone (2–5%), which can be removed without difficulty by distillation, is also formed.

(11) A. Dornow, I. Kühlcke, and F. Baxman, *Ber.*, **82**, 254 (1949).

(12) M. S. Newman, *Org. Synthesis*, Coll. Vol. III, 631 (1955).

(13) Boiling points are uncorrected.

(14) R. R. Dreisbach and R. A. Martin, *Ind. Eng. Chem.*, **41**, 2875 (1949).

(15) S. F. Birch, R. A. Dean, F. A. Fidler, and R. A. Lowry, *J. Am. Chem. Soc.*, **71**, 1362 (1949).

(16) George W. Gates and Co., Franklin Square, Long Island, N. Y.

Fluorine-Containing Nitrogen Compounds. II. Trimerization of Trifluoroacetonitrile[1]

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Received February 9, 1959

2,4,6-Tris(trifluoromethyl)-1,3,5-triazine was first synthesized by McBee, Pierce, and Bolt[3] by trimerization of trichloroacetonitrile in the presence of hydrogen chloride and subsequent fluorination of the trimer. This method was improved somewhat by Norton.[4] More recently Reilly and Brown[5] have described the high-pressure, high-temperature trimerization of trifluoroacetonitrile in the absence of catalysts. The yield of triazine based on unrecovered nitrile was 45–60% but the conversion was only about 30%.

Although these workers have shown that no catalyst is necessary to effect trimerization of perfluoroalkyl nitriles, we have found that the use of hydrogen chloride as a catalyst produces much more satisfactory results. Yields in excess of 90%, based on nitrile charged, have been achieved at modest pressures and temperatures. Boron trifluoride was found to be ineffective at low tempera-

(1) This work was performed under the auspices of the U.S. Atomic Energy Commission.

(2) Present address: Department of Chemistry, University of California, Los Angeles, Calif.

(3) E. T. McBee, O. R. Pierce, and R. O. Bolt, *Ind. Eng. Chem.*, **39**, 391 (1947).

(4) T. R. Norton, *J. Am. Chem. Soc.*, **72**, 3527 (1950).

(5) W. L. Reilly and H. C. Brown, *J. Org. Chem.*, **22**, 698 (1957).

tures as a catalyst.[6] Table I lists yields of crude trimer obtained at various temperatures with three different ratios of nitrile to hydrogen chloride. It is interesting to note that with a nitrile to hydrogen chloride ratio of 4 or 5 to 1 there is a marked decrease in yield as the temperature of reaction is raised. With lower ratios this effect is less pronounced. We interpret this an indication that the initial step in the trimerization is a rapid, reversible equilibrium between the nitrile and hydrogen chloride, which is shifted toward the two components as the temperature increases.

TABLE I

Millimoles			Temp.,	Recovery, Millimiles		% Recovery	%
CF_3CN[a]	HCl[a]	Ratio	°C.	Gas[a]	Liq.[b]		Yield
32.35	8.1	4.0	[c]	11.6	26.9	95.3	83.3
32.41	8.1	4.0	100		15.0		46.3
31.81	7.7	4.1	100	26.5	11.8	97.0	37.0
32.08	6.3	5.1	150	32.5	5.3	98.3	16.4
32.58	6.4	5.1	150	32.9	4.5	96.1	13.9
31.9	15.7	2.0	[c]	16.0	25.6	87.4	80.0
32.4	16.2	2.0	100	22.9	21.9	92.1	67.6
32.1	32.2	1.0	[c]	20.3	30.2	78.7	94.1
32.9	32.2	1.0	100		28.2		85.7
31.7	32.1	1.0	125	36.7	23.8	94.8	75.0
33.0	32.7	1.0	150	37.1	24.7	94.1	74.9
32.7[d]	32.1	1.0	[c]	33.1	18.8	80.2	57.7

[a] Calculated from P-V-T measurements assuming an ideal gas. [b] Millimoles of nitrile appearing as trimer. [c] Room temperature which varied from about 10 to 30°. [d] This experiment was run in a 100-ml. Parr high-pressure hydrogenation bomb.

EXPERIMENTAL

Trifluoroacetonitrile was prepared by dehydration of trifluoroacetamide according to the procedure of Gilman and Jones.[7] Hydrogen chloride and boron trifluoride were taken from Matheson Co. cylinders, frozen in liquid nitrogen in a glass trap and outgassed to remove a small amount of noncondensable material.

Trimerizations were effected in a 25-ml. bomb made from a $5^1/_2$-in. length of 1-in. diameter stainless steel rod with a $^5/_8$-in. hole drilled to a depth of 5 in. The end was threaded to take a No. 55-660 Matheson needle valve. A $^1/_{16}$-in. thick Teflon gasket was used to ensure a vacuum-tight seal. The outlet of the needle valve was fitted with an 18-mm. brass ball which allowed direct connection to a standard glass vacuum manifold. The reactants were measured as gases in a calibrated bulb with a Wallace and Tiernan model FA 160 absolute pressure gage having a range of 0–400 mm. of Hg. They were condensed in the previously evacuated and outgassed bomb by means of liquid nitrogen. The valve was then closed, the bomb allowed to warm to room temperature and maintained at the specified temperature for 18–20 hr. Temperatures between 100 and 150° were maintained to ±5° by a stirred oil bath. The bomb was then cooled to room temperature, if necessary, and reconnected to the vacuum manifold. The contents were pumped slowly through two traps in series, the first at −78° and the second at −196°. The amount of material in the −196° trap (listed in Table I as millimoles of recovered gas) was measured gasometrically. Infrared analysis showed it to consist mainly of HCl with varying amounts of unreacted nitrile. In many of the spectra a very weak doublet appeared at 5.5–5.6μ in the C=C or C=N region. This band is, at present, unassigned and could be due to traces of either a by-product or of one of the reaction intermediates. Several attempts at concentration of the species responsible were unproductive. The material from the −78° trap was vacuum distilled into a tared tube and weighed. It consisted primarily of trimer contaminated by a little HCl, which could be removed either by washing with aqueous sodium carbonate or by vacuum distilling the vapors through a small bed of ascarite. The latter proved to be more convenient on a small scale. Linde Molecular Sieve type 5A was less effective. A typical sample of trimer had n_D^{25} 1.32208, $d_{23.5}$ 1.595 (reported n_D^{25} 1.3161,[5] 1.3231[3]; d_{25} 1.593[5]; d_{26} 1.5857[3]).

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(6) R. T. Foster, U.S. Patent 2,375,545 (1945), reports preparation of 2,4,6-tris(trichloromethyl)-1,3,5-triazine together with monomer and tetramer by passing chlorine and and acetonitrile over carbon impregnated with halides of zinc, copper, or an alkaline earth metal at 200–400°.

(7) H. Gilman and R. G. Jones, *J. Am. Chem. Soc.*, 65, 1458 (1943).

Kojic Acid and α-Chloro-α-deoxykojic Acid in Reactions Catalyzed by Sulfuric Acid and Potassium Acetate

L. L. WOODS[1] AND P. A. DIX

Received February 11, 1959

In several previous communications[2,3] new reactions of 4-pyrones have been revealed by attempting to ascertain to what extent these compounds exhibit an aromatic character. To this end it was decided to determine if nuclear hydroxy-4-pyrones such as kojic acid and α-chloro-α-deoxykojic acid would participate in the Pechmann[4] reaction.

The reaction of kojic acid with citric, malic, and maleic acids in the presence of concentrated sulfuric acid reveals that the Pechmann reaction does take place to form pyrono-coumarins but the products are highly contaminated compounds which are difficult to isolate and still more difficult to purify. Compound I was the only one produced in anything like satisfactory purity and yields. Infrared data were not sufficient for a decision as to the true nature of such a complicated compound, due to the fact that the pyrone carbonyl, nonnuclear carbonyl, lactone groupings, and esters all absorb frequencies in the near vicinity of each other. However, the formation of coumarins by the reaction of phenols with malic acid and under Pechmann conditions is well known and no further investigation on the nature of the compound is presented due to the fact that the syn-

(1) The person to whom all communications regarding this paper should be directed.

(2) L. L. Woods, *J. Am. Chem. Soc.*, 77, 3161 (1955).

(3) L. L. Woods, *J. Org. Chem.*, 22, 341 (1957).

(4) R. Adams, *Org. Reactions*, 7, 1 (1954).

TABLE I

ACYL DERIVATIVES OF α-CHLORO-α-DEOXYKOJIC ACID

No.		M.P., °C.	% Yield	Formula	Calcd. Carbon	Calcd. Hydrogen	Found Carbon	Found Hydrogen
II_A	Acetate	96–97	94	$C_8H_7ClO_4$	47.42	3.48	47.64	3.70
II_B	Cinnamate	150	98	$C_{15}H_{11}ClO_4$	61.97	3.81	61.84	3.64
II_C	Phenoxyacetate	96–97	100	$C_{14}H_{11}ClO_5$	57.05	3.76	56.87	3.97
II_D	Benzoate	119–120[a]	89	$C_{13}H_9ClO_4$	58.99	4.18	58.79	3.97

[a] Agrees well with 117–118° reported by T. Yabuta, *J. Chem. Soc.*, **125**, 575 (1924).

TABLE II

No.	Compound	Acyl Der.	M.P., °C.	Formula	Calcd. Carbon	Calcd. Hydrogen	Calcd. Chlorine	Found Carbon	Found Hydrogen	Found Chlorine
III_A	2-(Acetoxymethyl)-6-methylpyrano [3, 2-*b*] pyran-4, 8-dione	Kojic acid acetate	102 & 105[a]	$C_{12}H_{10}O_6$	57.60	4.02		57.12	4.36[b]	
III_B	2-(Chloromethyl)-6-methylpyrano[3, 2-*b*]-pyran-4,8-dione	II_A	106	$C_{10}H_7ClO_4$	52.99	3.11	15.64	52.61	4.23	15.47[c]
III_C	2-(Chloromethyl)-6-methyl-7-phenoxypyrano-[3,2-*b*]pyran-4,8-dione	II_C	102–103	$C_{16}H_{11}ClO_5$	60.29	3.47	11.12	59.99	3.74	10.94

[a] See preparation of compound VI from V. [b] Second run: C, 57.74; H, 3.97. [c] Second run: C, 52.84; H, 4.43; Cl, 15.49.

thesis was abandoned because the reaction did not lend itself to the preparation of the homologs of 2-hydroxymethylpyrano[3,2-*b*]pyran-4,6-dione (I).

Since the Pechmann reaction with kojic acid and α-chloro-α-deoxykojic acid left much to be desired it was decided to try the effect of fused potassium acetate on acyl derivatives of the two pyrones mentioned above. It was visualized that if the potassium acetate could effect a rearrangement of the acyl radical in the 5 position, then a Kostanecki-Robinson[5] type of cyclization might then be induced.

In order to demonstrate the postulated reaction, some new acyl derivatives of α-chloro-α-deoxykojic acid were prepared to be used as starting materials. These compounds were listed in the II_{A-D} series.

The postulated effect of fused potassium acetate on the acyl derivative was supported by experiment in two of the three compounds tested as witnessed by formation of compounds III_A, III_C; but III_B, unaccountably, was unsatisfactory since its hydrogen was 1.1–1.3% high.

In order to verify the suggested course of the reaction, a compound previously reported[6] and described as being *principally* 2-acetoxymethyl-5-hydroxy-6-acetyl-4-pyrone (V) was prepared. This time the compound was rigorously purified and compared with IV, the product obtained by rearrangement of kojic acid diacetate. The compounds were found to be identical by mixture melting point and infrared spectra.

The cyclization procedure used to prepare compounds of the III_{A-C} series was applied to compound V. A cyclized product VI identical with III_A was obtained. Compound VI had a somewhat higher melting point than the original III_A but since no depression was observed in the mixture melting point and since neither compound showed any difference in infrared spectra, there is no doubt that they are the same substance.

TABLE III

SIGNIFICANT INFRARED ABSORPTION BANDS[a] ($Cm.^{-1}$)

III_A	1235, 1453, 1629, 1667, 1739
III_B	1379, 1429, 1637, 1669, 1751
III_C	1605, 1639, 1672, 1761, 1497

[a] Infrared spectra determined from KBr pellets on Beckman IR-5 instrument.

EXPERIMENTAL[7]

Preparation of 2-hydroxymethylpyrano[3,2-b]pyran-4,6-dione, [I]. Seven and one tenth g. (0.05 mole) of kojic acid was thoroughly mixed with 20 ml. of concentrated sulfuric acid. To this mixture was added 6.7 g. of malic acid (0.05 mole). The mixture was shaken and the flask immersed in an oil bath at 120–130° and heated at this temperature for 3 hr.

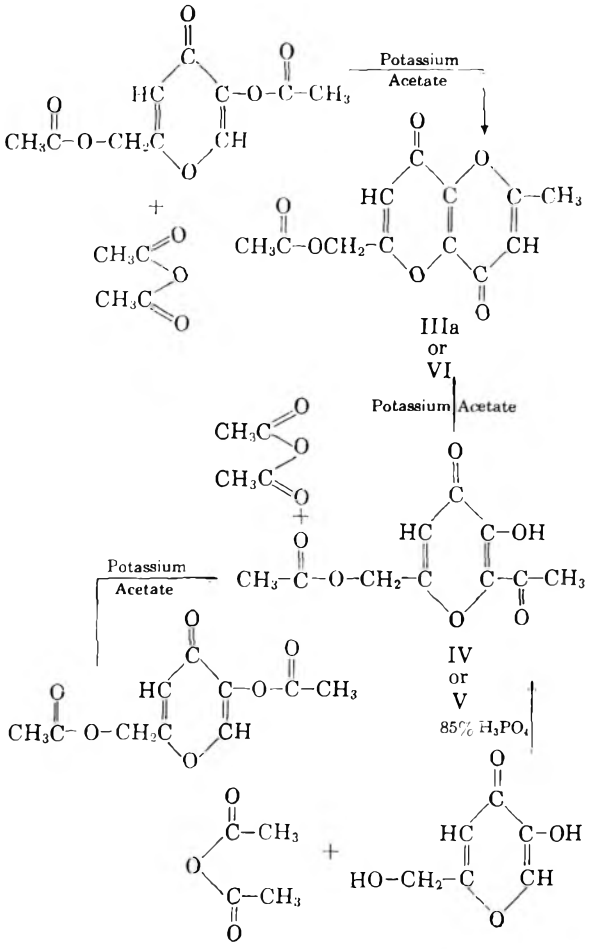
Occasional shaking of the flask appeared to assist the reaction. At the termination of the reaction period the mixture was cooled, 100 ml. of water was added, the solution nearly neutralized with sodium bicarbonate, and then extracted with three 100-ml. portions of ethyl acetate. Evaporation of the solvent over a steam bath left the product, 6.7 g., which was recrystallized twice from absolute ethanol, m.p. 174–175°.

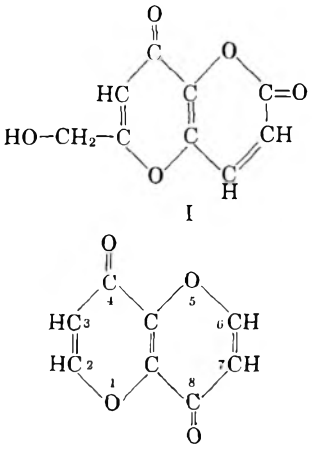
Anal. Calcd. for $C_9H_6O_5$, C, 55.69; H, 3.11. Found: C, 55.29; H, 3.16.

(5) R. C. Elderfield, *Heterocyclic Compounds*, John Wiley and Sons, New York, N. Y., 1951, Vol. 2, pp. 176, 234.

(6) L. L. Woods, *J. Am. Chem. Soc.*, **75**, 3608 (1953).

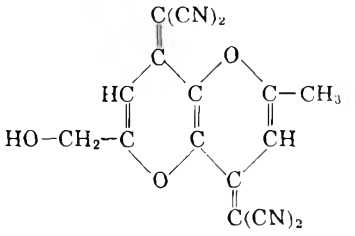
(7) All analyses and molecular weight determinations were performed by Dr. Carl Tiedcke, Teaneck, N. J. Melting points were run on a Fisher-Johns melting point assembly.





I

Pyrano[3,2-*b*]pyran-4,8-dione
Basic structure III_{A-C} series



Malononitrile derivative III_A

The infrared spectrum was determined on a Beckman IR-5 instrument. KBr pellet gave the following significant absorption bands: 1757 (broad), 1667, 1656, 1613 cm.$^{-1}$

Preparation of acyl derivatives of α-chloro-α-deoxykojic acid [II_{A-C} series]. To 100 ml. of benzene was added 0.06 mole of chlorodeoxykojic acid followed by 0.06 mole of the acyl halide. The mixture was usually refluxed 2 hr., but for the benzoyl derivative the reflux period was overnight, the solution filtered through a hot funnel, and the benzene removed over a steam bath. The analytical samples were all recrystallized twice from boiling heptane. Compounds of this series are listed in Table I.

Preparation of pyrano [3,2-b]-pyran 4,8-diones [III_{A-C} series]. Equal weights (12 g.) of the acylated pyrone (II_{A-D} series and kojic acid diacetate), potassium acetate, and acetic anhydride were mixed and the flask loosely stoppered with cotton. The mixtures were in each case heated for 2 hr. in a Fisher Hi-Temp oil bath at 120–130°. The melts were cooled, diluted with about 50 ml. of water, the solution neutralized with sodium bicarbonate, and then chilled. The precipitate was filtered with suction and dried in air. Crude yields from the three experiments exceeded theoretical slightly because of entrapped salts, which also added to the difficulty of drying the precipitates. Analytical samples were obtained by recrystallizing the compounds twice from absolute ethanol. Table II lists the products of this series. The cinnamic and benzoic acyl derivatives of α-chloro-α-deoxykojic acid failed to cyclize.

Malononitrile derivative of III_A. One g. each of III_A and malononitrile were refluxed together in 10 ml. of acetic anhydride for 30 min. The solution was diluted with 50 ml. of water, neutralized with sodium bicarbonate, and the solution extracted with benzene. Evaporation of the solvent produced 1.6 g. of red crystals. Recrystallization of the compound from 100 ml. of boiling heptane produced flesh-colored crystals, m.p. 101–102°.

Anal. Calcd. for $C_{18}H_{10}N_4O_4$: N, 16.18. Found: N; 15.97.

Repeated attempts to obtain a malonitrile derivative[8] from I_A or coumarin failed.

2-Acetoxymethyl-5-hydroxy-6-acetyl-4-pyrone [IV]. A mixture consisting of 12 g. of kojic acid diacetate and 12 g. of potassium acetate was heated at 130–135° for 90 min. in a Fisher Hi-Temp oil bath. The mixture was then cooled, diluted with 50 ml. of water, and the resulting solution extracted with ethyl acetate. Evaporation of the solvent produced 3.3 g. of brown crystals. The material was recrystallized twice from ethanol and then sublimed, m.p. 137.5°. The compound gave an immediate and intense red coloration with a 2% solution of ferric chloride.

Anal. Calcd. for $C_{10}H_{10}O_6$: C, 53.10; H, 4.45; mol. wt., 226.19. Found: C, 52.74; H, 4.25; mol. wt., 217, 211, 229, 223 (Rast).

A sample of 2-acetoxymethyl-5-hydroxy-6-acetyl-4-pyrone (V) was prepared by a procedure previously described[6] but this time the compound was purified by suspending a sample in a dilute sodium bicarbonate solution to remove all traces of acetic acid and dried in air. The first half of the analytical sample, 1 g., was sublimed and this sublimate discarded. The sublimate of the residual portion of the sample was retained. The compound gave a red coloration with $FeCl_3$ and melted at 137°. The mixture m.p. with compound IV was 136–138°, infrared spectra of compounds IV and V were identical.

A mixture consisting of 12 g. each of compound V, fused potassium acetate, and acetic anhydride was heated for 2 hr. at 120–130° in an oil bath to prepare 2-acetoxymethyl-6-methylpyrano[3,2-b]pyran-4,8-dione (VI) by an alternate route. The resulting compound (8.5 g.) was purified by extracting about 2 g. with 100 ml. of boiling heptane. The solvent was discarded. The residue was extracted with a second 100-ml. portion of heptane which upon chilling gave colorless prisms, m.p. 105°. A mixture melting point of 102–103°

(8) L. L. Woods, *J. Am. Chem. Soc.*, **80**, 1440 (1958).

was determined using samples of VI and III_A. The two compounds gave identical infrared spectra.

Anal. Calcd. for $C_{12}H_{10}O_6$: C, 57.60; H, 4.02. Found: C, 57.92; H, 3.52.

Acknowledgment. The author wishes to acknowledge with thanks, the financial assistance of the Robert A. Welch Foundation.

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Structure Proof of 2,6-Di-*t*-butylpyridine-3-sulfonic Acid by Proton Magnetic Resonance

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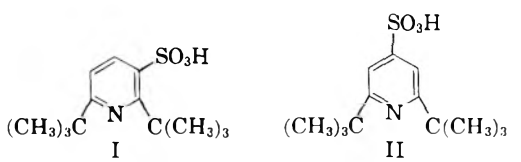
Received February 12, 1959

In contrast to ordinary pyridine bases, 2,6-di-*t*-butylpyridine undergoes ready sulfonation[1] by sulfur trioxide in liquid sulfur dioxide at $-10°$. Because of the large steric effect anticipated for a sulfonic acid substituent ortho to a *t*-butyl group, the original authors suggest that perhaps the substituent enters the pyridine ring in the 4- position rather than in the 3- position, as is customary for simple pyridine bases under vigorous conditions. Recently den Hertog[2] found that this sulfonic acid is rather inert to hydrolysis, and from this and from the properties of the hydrolysis product he concluded that it must be the 3- and not the 4- derivative. Although the likelihood of a molecular rearrangement during the hydrolysis is considered small, it seemed worthwhile to test this conclusion by examining the nuclear magnetic resonance (NMR) spectrum of the sulfonic acid itself. The results show unequivocally that the material is indeed the 3-sulfonic acid.

The NMR technique is particularly helpful when chemical evidence is available that rules out all but a small number of structures for the unknown material. In the present instance, it was anticipated that a decision between formulas I and II could readily be made because the difference in symmetry of these two structures should lead to several clearcut differences in their NMR spectra.



Structure I contains a pair of structurally nonequivalent protons attached to the ring. These should give rise to two resonance signals, each perhaps split into a doublet by their mutual electron-coupled spin-spin interaction. In structure II, the ring protons are equivalent and should produce a single, sharp peak. Similarly, I has two nonequivalent *t*-butyl groups, while both are equivalent in II. Thus structure I should show a second pair of peaks, each about nine times as strong as one of the ring-proton signals, while structure II should have only one strong peak at the field-value corresponding to methyl protons. The acid hydrogen in either molecule should contribute an additional peak comparable in strength with that of the ring-protons.

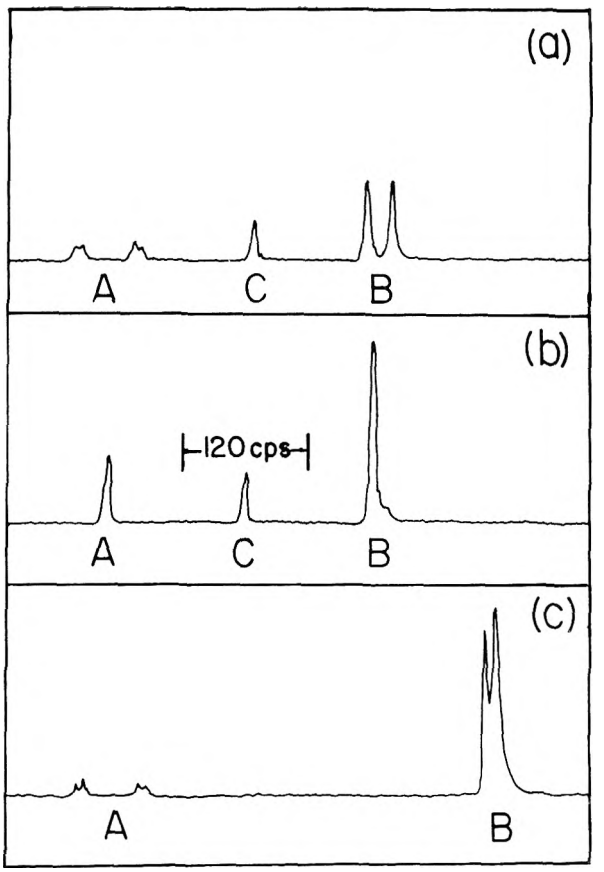


Fig. 1. NMR spectra of the sodium salts of 2,6-lutidine-3-sulfonic acid (a) and of 2,6-lutidine-4-sulfonic acid (b) in D_2O, and spectrum of 2,6-di-*t*-butylpyridine-3-sulfonic acid in liquid SO_2 (c). Peaks at A are due to ring protons, at B to methyl or *t*-butyl group protons, and at C to H_2O. The magnetic field increases towards the right for each trace.

To confirm this reasoning, we first obtained the spectra of authentic samples[3] of the two 2,6-lutidinesulfonic acids analogous to I and II. The spectra, shown in Figs. 1(a) and 1(b), have precisely the anticipated features. The samples consisted of solutions containing 2 moles of the acid

(1) H. C. Brown and B. Kanner, *J. Am. Chem. Soc.*, **75**, 3865 (1953).

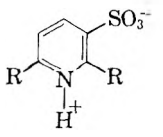
(2) H. J. den Hertog, *Chem. Weekblad*, **53**, 560 (1957).

(3) R. F. Evans and H. C. Brown, to be published.

and 1 mole of sodium carbonate per liter of D_2O, so that the observed spectra are those of the sulfonate ions and of a small amount of H_2O formed when the acid is neutralized.

A usable sample of the 2,6-di-*t*-butylpyridinesulfonic acid could not be obtained in the analogous way because of the unexpectedly low water-solubility of the sodium salt. The solvent finally found most suitable was that used originally[1] in the sulfonation reaction, liquid sulfur dioxide. Sealed sample tubes containing liquid sulfur dioxide may safely be stored, and examined, at room temperature, and the solvent is ideal in that it produces no proton spectrum which would obscure that of the solute. Since the lutidinesulfonic acids are insoluble in liquid sulfur dioxide, the three spectra could not be compared in identical solvent, and therefore no attempt was made to measure the chemical shifts of the various peaks relative to a fixed standard. However, the spectrum of the 2,6-di-*t*-butylpyridinesulfonic acid, shown in Fig. 1(c), leaves no doubt that the material has structure I and not structure II.

An interesting feature of the latter spectrum is the apparent absence of a signal for the acid proton. The most likely explanation appears to be that structure I in liquid sulfur dioxide is in equilibrium with the dipolar ionic structure III, and that the



III

rate of migration of the proton is such as to result in a considerably broadened line[4] which would probably be undetected because of the small concentration of this species of proton.

Acknowledgment. All spectra were obtained with a Varian model 4311 high resolution NMR spectrometer operating at 56.4 mc. We should like to thank the Purdue Research Foundation, E. I. du Pont de Nemours and Co., and the National Science Foundation for grants which made the purchase of this equipment possible. We also wish to thank Professor H. C. Brown for calling this problem to our attention and providing the compounds.

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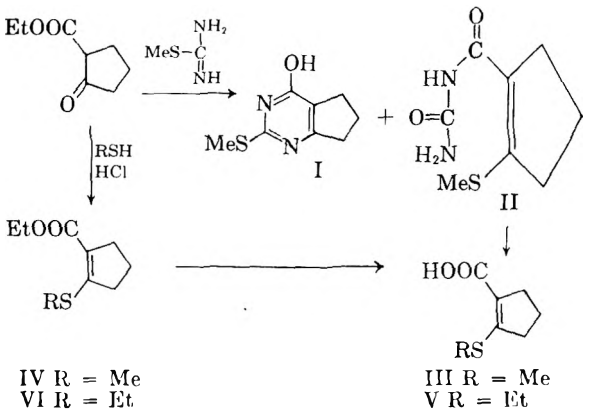
(4) See J. D. Roberts, *Nuclear Magnetic Resonance*, McGraw-Hill Book Co., Inc., New York, New York, 1959, p. 63.

Potential Anticancer Agents.[1] XXI. 2-(Alkylthio)cyclopentene-1-carboxylic Acids and Derivatives

LEONARD O. ROSS, LEON GOODMAN, AND B. R. BAKER

Received February 12, 1959

An earlier paper in this series[2] described the condensation of 2-methyl-2-thiopseudourea and 2-carbethoxycyclopentanone in aqueous alkali which led to the isolation of the expected 4-hydroxy-2-(methylthio)-5,6-trimethylenepyrimidine (I) and a product to which structure II was tentatively assigned. Some further work, which is reported in this note, has placed the structural assignment of II on firmer ground.



Alkaline hydrolysis of the compound assigned structure II gave a carboxylic acid which had strong ultraviolet absorption at 287 mμ, in good agreement with the absorption expected for compound III.[3] For comparison, the acid (III) was synthesized from 2-carbethoxycyclopentanone by the method used by Posner to synthesize 3-(ethylthio)crotonic acid.[4] Methanethiol, in large excess, on reaction with 2-carbethoxycyclopentanone in the presence of concentrated hydrochloric acid, furnished, as the directly isolated product, ethyl 2-(methylthio)cyclopentene-1-carboxylate (IV). The ester IV was saponified to the acid III, which was identical with acid III derived from II as shown by nondepression of the mixed melting point, identical infrared spectra, and the same paper chromatographic behavior. It is interesting to note that the ester IV was the direct product from the reaction of

(1) This work was carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, Contract No. SA-43-ph-1892. For the preceding paper of this series, *cf.* W. A. Skinner, H. F. Gram, C. W. Mosher, and B. R. Baker, *J. Am. Chem. Soc.*, in press.

(2) L. O. Ross, L. Goodman, B. R. Baker, paper XVII of this series, *J. Am. Chem. Soc.*, **81**, 3108 (1959).

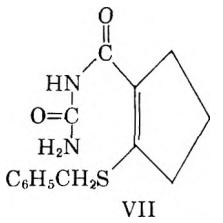
(3) B. R. Baker, M. V. Querry, and A. F. Kadish, *J. Org. Chem.*, **13**, 123 (1948).

(4) T. Posner, *Ber.*, **32**, 2801 (1899).

methanethiol and 2-carbethoxycyclopentanone, whereas Posner[4] showed that in the similar reaction of acetoacetic ester, the first product was the thioketal, which was converted to the 3-(alkylthio)-crotonic acid only after vigorous saponification.

Similarly, ethanethiol with 2-carbethoxycyclopentanone gave a good yield of the ester VI, which could be saponified to the acid V. Several attempts to effect a condensation between 2-ethyl-2-thiopseudourea and 2-carbethoxycyclopentanone, so as to obtain the ethyl analogs of I and II, were unsuccessful.

When the reaction of 2-methyl-2-thiopseudourea and 2-carbethoxycyclopentanone was carried out in the presence of benzyl mercaptide ion,[5] a compound was isolated whose analysis, infrared and ultraviolet absorption spectra, and paper chromatographic behavior indicated it to be the benzyl analog of II, [2-benzylthio)cyclopentene-1-carbonyl]-urea (VII). This strongly indicates that the compound II previously isolated[2] was not the product of an intramolecular rearrangement but resulted from the intervention of methyl mercaptide ion, which would be present in the alkaline reaction mixture containing 2-methyl-2-thiopseudourea.



VII

Although the detailed mechanism of formation of II would be of interest, the results have been presented here since no further work in this area is contemplated.

EXPERIMENTAL[6]

2-(Methylthio)cyclopentene-1-carboxylic acid (III). A. *By hydrolysis of* II. A mixture of 2.00 g. (10.0 mmoles) of II,[2] 4.0 g. (64 mmoles) of potassium hydroxide (85%), and 40 ml. of water was heated under reflux for 1 hr. The resulting solution was filtered and the filtrate was adjusted to *p*H 5 with glacial acetic acid. The precipitated product, 0.50 g. (31%), m.p. 190–200° (dec.), was dissolved in 50 ml. of saturated aqueous sodium bicarbonate, the solution was filtered, and the filtrate adjusted to *p*H 5 with glacial acetic acid. The purified product, 0.30 g. (19%), m.p. 234–237° (dec.), was homogeneous on paper chromatography,[7] with R_{Ad} = 1.38, and had $\lambda_{max(\mu)}^{KBr}$ 3.7–3.9 (carboxyl OH), 6.06 (carboxyl C=O), 6.41 (C=C), 7.02 and 10.59 (COOH), and $\lambda_{max(\mu)}$ 287 (ϵ 11,400) in 95% ethanol.

Anal. Calcd. for $C_7H_{10}O_2S$: C, 53.1; H, 6.38; S, 20.2. Found: C, 53.0; H, 6.60; S, 19.9.

B. *By saponification of* IV. A mixture of 5.0 g. (27 mmoles) of ethyl 2-(methylthio)cyclopentene-1-carboxylate (IV) (*cf.* below), 5.0 g. (78 mmoles) of potassium hydroxide (85%), and 75 ml. of water was heated under reflux for 1.5 hr. The resulting solution was filtered and the filtrate was adjusted to *p*H 5 with glacial acetic acid. The precipitated product, 2.0 g. (46%), m.p. 170–210° (dec.), was dissolved in 30 ml. of saturated aqueous sodium bicarbonate, the solution filtered, and the filtrate acidified to *p*H 5 with glacial acetic acid. The purified product, 0.60 g. (14%), m.p. 232–237° (dec.), had m.p. 234–237° (dec.) when mixed with acid prepared by hydrolysis of II. Its infrared spectrum was identical with that described above and it showed the identical paper chromatographic behavior.

No effort was made to increase the yield in the above reaction.

Ethyl 2-(methylthio)cyclopentene-1-carboxylate (IV). A mixture of 10.0 g. (64 mmoles) of 2-carbethoxycyclopentanone, 11.5 g. (0.24 mole) of methanethiol, and 10 ml. of concentrated hydrochloric acid was stirred for 4 hr. at −5 to 0°. The solution was extracted with 100 ml. of methylene chloride. The extract was chilled, causing the precipitation of 0.20 g. of acid III, m.p. 235–237° (dec.), which was removed by filtration. The filtrate was evaporated *in vacuo*, leaving a solid residue, 4.0 g. (34%), m.p. 45–48°. This product was recrystallized twice from methanol with the use of Norit, giving the analytical product, 3.8 g (32%), m.p. 68–70°; $\lambda_{max(\mu)}^{KBr}$ 5.97 (carbonyl C=O), 6.39 (C=C), 7.75–8.45 (several bands which probably represent ester C—O—C).

Anal. Calcd. for $C_9H_{14}O_2S$: C, 58.0; H, 7.55; S, 17.2. Found: C, 58.0; H, 7.86; S, 17.5.

Ethyl 2-(ethylthio)cyclopentene-1-carboxylate (VI). A mixture of 15.0 g. (96 mmoles) of 2-carbethoxycyclopentanone, 11.9 g. (0.19 mole) of ethanethiol, and 30 ml. of concentrated hydrochloric acid was stirred at room temperature for 2 hr. The mixture was extracted with 50 ml. of methylene chloride, the extract was evaporated *in vacuo*, and the residue was distilled using a short Vigreux column. The product, 13.3 g. (77%), was collected at 110° (0.3 mm.); n_D^{20} 1.5341; $\lambda_{max(\mu)}^{film}$ 5.90 (ester C=O), 6.36 (C=C), 7.92 (probably ester C—O—C).

Anal. Calcd. for $C_{10}H_{16}O_2S$: C, 59.9; H, 8.04; S, 16.0. Found: C, 59.9; H, 8.10; S, 15.9.

2-(Ethylthio)cyclopentene-1-carboxylic acid (V). A mixture of 5.0 g. (20.9 mmole) of VI, 5.0 g. (0.13 mole) of sodium hydroxide, and 50 ml. of water was heated, with stirring, on the steam bath for 1.5 hr. The cooled solution was extracted with 30 ml. of methylene chloride and the extract was discarded. The aqueous solution was decolorized with Norit and filtered. The filtrate was adjusted to *p*H 5 with glacial acetic acid, precipitating 0.40 g. (9.3%) of product, m.p 157–162°. The product was dissolved in 30 ml. of saturated aqueous sodium bicarbonate, treated with Norit, filtered, and the filtrate adjusted to *p*H 5 with glacial acetic acid, precipitating 0.30 g. (6.9%) of solid, m.p. 174–175°; $\lambda_{max(\mu)}^{KBr}$ 3.95 (carboxyl OH), 6.11 (carboxyl C=O), 6.49 (C=C), 7.77 and 10.58 (COOH); $\lambda_{max(\mu)}$ (ϵ 11,600) in 95% ethanol.

Anal. Calcd. for $C_8H_{12}O_2S$: C, 55.7; H, 7.01; S, 18.6. Found: C, 55.5; H, 7.03; S, 18.3.

The yield of acid V could probably be improved by the use of more severe hydrolytic conditions.

[*2-(Benzylthio)cyclopentene-1-carbonyl*]*urea* (VII). To a stirred solution of 27.8 g. (0.100 mole) of 2-methyl-2-thiopseudourea sulfate, 13.2 g. (0.200 mole) of potassium hydroxide (85%), and 150 ml. of water was added, dropwise during 1 hr., a mixture of 15.6 g. (0.100 mole) of 2-carbethoxycyclopentanone and 24.8 g. (0.200 mole) of α-toluenethiol. The reaction mixture was stirred for 8 hr. more and the solid present was removed by filtration. The solid was stirred with 200 ml. of methylene chloride, the resulting sus-

(5) This experiment was suggested by Mr. J. I. DeGraw, Jr., of These Laboratories.

(6) Boiling points and melting points are uncorrected; the latter were obtained with the Fisher-Johns apparatus.

(7) Paper chromatograms were run by the descending technique on Whatman No. 1 paper in the solvent system 1-butanol/acetic acid/water (5/2/3).[8] The spots were detected with ultraviolet light and are located relative to adenine, *i.e.*, $R_{Adenine}$ = 1.00.

(8) D. M. Brown, A. Todd, and S. Varadarajan, *J. Chem. Soc.*, 2388 (1956).

pension was filtered, and the solid was extracted with 100 ml. of hot (90°) methyl Cellosolve, some insoluble inorganic material being filtered. To the methyl Cellosolve filtrate was added 50 ml. of water and the solution was chilled yielding 1.0 g. (3.6%) of product, m.p. 188–190° (dec.). The solid was crystallized twice from 100 ml. of methanol with the aid of Norit to give 0.80 g. (2.9%) of pure VII, m.p. 190–193° (dec.), which was homogeneous on paper chromatography[8] with R_{Ad} = 1.47, and had $\lambda_{max(\mu)}^{KBr}$ 2.95–3.10 (NH), 5.90 and 6.12 (amide and urea carbonyls), 6.02 (NH_2), 6.48 (NH and C=C), 13.03 and 14.15 (monosubstituted phenyl), and $\lambda_{max(m\mu)}$ 307 (ϵ 12,500) in 95% ethanol.

Anal. Calcd. for $C_{14}H_{16}N_2O_2S$: C, 60.8; H, 5.83; S, 11.6. Found: C, 60.6; H, 5.71; S, 10.6, 10.7.

No effort was made to recover compound I from the filtrate from VII.

Acknowledgment. The authors wish to thank Dr. Peter Lim for interpretation of the infrared spectra and his staff for the paper chromatography.

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Preparation of Quinone Sulfenimines

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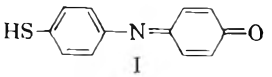
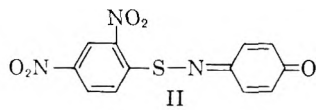
Received February 12, 1959

As a part of an investigation of the preparation of compounds of the thio indophenol series, attempts were made to prepare compound I



I

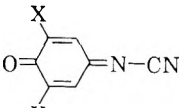
following the procedure of Hirsch[1] by reaction of *N*-chloro-*p*-quinoneimine with aromatic thiols unsubstituted in the para position. The desired compound was not obtained; but instead the reaction took another course to yield quantitatively, quinone sulfenimines. Since this method offers a simple procedure for the preparation of sulfenimines, the results are reported here. Gebauer-Fülnegg and Beatty[2] prepared a metallic complex of 4-chloro-2-nitrophenyl quinone sulfenimine by oxidation of the corresponding sulfenamide with sodium dichromate in acetic acid. By a similar oxidation procedure, Burmistrov and Glazkov[3] reported the preparation of a dinitro sulfenimine (II).



II

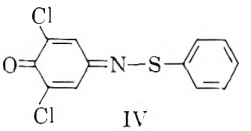
Other workers[4] noted that the reaction of thiols with *N*-chloroquinoneimine yielded colored products which could serve as quantitative estimations of the thiol in solution. Although the formation of quinone sulfenimines was postulated, no attempts were made to isolate or characterize the colored products.

When one equivalent of *N*-chloroquinoneimine was added, with rapid stirring, to the aryl thiol dissolved in sodium carbonate solution, a vigorous reaction occurred yielding a deep red insoluble precipitate. The product was insoluble in dilute alkali and dilute mineral acid and soluble in organic solvents. When treated with alkaline sodium cyanide, the quinone sulfenimine decomposed with the liberation of the thiol which could be detected by odor. Concomitantly, a deep green, unstable water soluble dye was formed, presumably, compound III.



III. X = H, Cl, Br

The infrared spectrum of compound IV



IV

shows absorption maxima at 6.05, 6.45, 6.85 (doublet), 7.85 (doublet), 9.55, 11.1, 12.27, and 13.53μ indicative of quinoid carbonyl and *p*-substituted aromatics. The absence of an absorption peak at 4.0μ due to SH indicates that no free thiol is present.

Similar reactions of *N*-chloroquinoneimines with a variety of thiols such as ethyl potassium xanthate, 2-mercaptobenzothiazole yielded the corresponding sulfenimine (see Table I).

In an attempt to obtain an intramolecular rearrangement of the quinone sulfenimine to the corresponding thio indophenol similar to I, it was found that the reaction was effected by refluxing in glacial acetic acid. Other Lewis acids and bases either cleaved the molecule or had no effect upon it. The course of the rearrangement could be followed by treating sequential aliquots of the glacial acetic acid solution with dilute alkali and noting the appearance of the characteristic blue color of indophenols. The results of these studies will be reported at a later date.

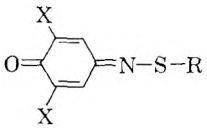
(1) A. Hirsch, *Ber.* **13**, 1903 (1880).

(2) E. Gebauer-Fülnegg and H. A. Beatty, *J. Am. Chem. Soc.* **49**, 1361 (1927).

(3) S. I. Burmistrov and V. I. Glazkov, *J. Gen. Chem. (USSR)*, **22**, 1901 (1952) Consultants Bureau Translation; *Chem. Abstr.*, **47**, 6367 (1953).

(4) W. R. Fearon, *Biochem. J.*, **38**, 399 (1944); R. A. McAllister, *J. Pharm. and Pharmacol.*, **3**, 506 (1951); R. A. McAllister, *J. Clin. Path.*, **4**, 432 (1952); R. A. McAllister and K. W. Howells, *J. Pharm. and Pharmacol.*, **4**, 259 (1952); C. E. Searle, *J. Appl. Chem.*, **5**, 313 (1955).

TABLE I

QUINONE SULFENIMINES 

X	R	M.P.	Compd.	Analysis Calcd. C	H	N	S	Found C	H	N	S
H	C_6H_5	97	$C_{12}H_9NOS$	67.0	4.2	6.5	14.9	67.0	4.2	6.8	15.0
Cl	$CH_2C_6H_5$	127–128	$C_{13}H_9Cl_2NOS$	52.4	3.0	4.7	10.7	52.2	3.3	—	10.9
Cl	C_6H_5	208	$C_{12}H_7Cl_2NOS$	50.7	2.5	4.9	11.3	50.7	2.4	5.1	11.9
Cl	2-Acetamidophenyl	243–246	$C_{14}H_{10}Cl_2N_2O_2S$	49.3	2.9	8.2	9.4	48.9	3.0	—	—
Cl	2-Benzimidazolyl	152–154	$C_{13}H_6Cl_2N_2OS_2 \cdot {}^1/_2H_2O$	44.6	2.0	8.0	18.3	44.6	2.1	—	18.6
Br	$C_2H_5OC(S)$—	170–173	$C_9H_7Br_2NO_2S_2$	28.1	1.8	3.6	16.6	28.6	1.9	4.1	16.5

EXPERIMENTAL

A solution of 0.01 mole of the appropriate *N*-chloro-*p*-quinoneimine in 3 ml. of dioxane was added to 0.01 mole of thiol in 10% sodium carbonate, cooled in an ice bath. If necessary, a small amount of dioxane was added to the thiol to ensure complete solution. A deep red precipitate immediately formed and was filtered and dried. It was recrystallized from ethanol-water or dioxane-water.

Table I lists the compounds prepared.

One hundredth mole of sulfenimine (2,6-dichloroquinone sulfenimine) was dissolved in 100 ml. of glacial acetic acid and kept at reflux temperature for 30 min. After cooling the solution was poured into ice water and the resulting precipitate was filtered. A portion of the solid thus obtained was treated with 10% sodium carbonate to give a blue-green solution which turned to deep blue on standing.

The infrared spectrum was obtained in a Perkin-Elmer double beam recording spectrophotometer.

Acknowledgment. The authors wish to express their gratitude to the Analytical Research Branch of the Research Directorate, U. S. Army Chemical Warfare Laboratories for the analyses reported herein.

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1,2,4-Triphenylbenzene

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Received February 12, 1959

1,2,4-Triphenylbenzene has been reported to melt at 109°,[1] 119–120°,[2] 99.5–100° and 119.5–120°,[3] and 101.5–102°.[4] Aside from products obtained in degradative studies, it has been prepared by reaction of 3,4-diphenyl-4-hydroxy-2-cyclopentenone (*I*) with styrene, decarbonylation and dehydrogenation;[1,3,4] by reaction of I with phenylacetylene;[3] and has been reported to result from trimerization of phenylacetylene in the presence of bis(triphenylphosphino)nickel dicarbonyl.[1]

We have synthesized this compound by the following diene reactions; 3,4-diphenylthiophene-1,1-dioxide and phenylacetylene; 2,5-diphenylthiophene-1,1-dioxide and phenylacetylene; and α-acetoxystyrene with 3,4-diphenylthiophene-1,1-dioxide, as well as by the reported[1] reaction of styrene with I. All gave the same product, m.p. 100°. This was converted to the form melting at 119–120° by seeding a melt with a sample kindly provided by Dr. A. Halleux, as has been observed by other investigators.[2,3]

The trimerization of phenylacetylene[1] was repeated, and produced the substance melting at 109°. Mixed melting point with the 100° compound was 100–107.8°. The infrared spectra of these two compounds were almost identical, with the exception of a strong band at 952 cm.$^{-1}$, a shoulder at 689 cm.$^{-1}$, and several weaker bands shown by the 109°, but not by the 100° compound. The ultraviolet spectra, however, showed marked differences except for a common λ_{max} of 258 mμ, the 109° material showing additional maxima at 280 and 335 mμ and a shoulder at 315 mμ.

These spectral differences suggested the presence of unsaturation in the 109° substance. This was confirmed by rapid decolorization of potassium permanganate in acetone at room temperature; the 100° compound is inert to permanganate in refluxing acetone.

The 109° material thus cannot be 1,2,4-triphenylbenzene. The similarity of the infrared spectra, the ultraviolet spectra, and analysis, however, permit the possibility that it is a complex of 1,2,4-triphenylbenzene with a related phenylacetylene derivative. Its ability to survive chromatographic purification does not eliminate this possibility.

The available evidence confirms the conclusion[2,3] that 1,2,4-triphenylbenzene exists in two crystalline forms, melting at 100° and 119–120°.

(1) J. D. Rose and F. S. Statham, *J. Chem. Soc.*, 69 (1950).
(2) A. Halleux and C. Hoogzand, private communication (1957).
(3) W. Herz and E. Lewis, *J. Org. Chem.*, **23**, 1646 (1958).
(4) T. L. Jacobs and M. H. Goodrow, *J. Org. Chem.*, **23**, 1653 (1958).

EXPERIMENTAL[5]

1,2,4-Triphenylbenzene. Preparation from 3,4-diphenylthiophene-1,1-dioxide. A mixture of 1.0 g. (0.0037 mole) 3,4-diphenylthiophene-1,1-dioxide[6] and 1.0 g. (0.0098 mole) of phenylacetylene was slowly heated to 135°, at which point a sudden vigorous evolution of sulfur dioxide occurred. After 1 hr. at 140–150° excess phenylacetylene was removed under reduced pressure, the residue dissolved in 1:1 benzene–petroleum ether (b.p. 30–60°) and passed through a column of activated alumina. Solvent was removed, the product dissolved in petroleum ether, chromatographed on alumina, and eluted with 1:4 benzene–petroleum ether The oily product was taken up in a small quantity of petroleum ether, from which it crystallized very slowly. After 19 days, 71.5 mg. (6.3%) of white granules, m.p. 97.5–98.5°, were collected. After two recrystallizations from methanol, fine white needles were obtained, m.p. 99.1–99.6°.

A very low yield of the same compound was obtained by refluxing 1.07 g. (0.0040 mole) 3,4-diphenylthiophene-1,1-dioxide and 0.71 g. (0.0044 mole) α-acetoxystyrene[7] in 5 ml. xylene for 4 hr., acidification, and repeated chromatographic purification.

1,2,4-Triphenylbenzene. Preparation from 2,5-diphenylthiophene-1,1-dioxide. A mixture of 0.461 g. (0.00172 mole) 2,5-diphenylthiophene-1,1-dioxide,[8] and 1.06 g. (0.0104 mole) phenylacetylene were heated in a xylene vapor bath for 11 hr.; sulfur dioxide was evolved. The solution was diluted with petroleum ether, chromatographed on alumina and eluted with 1:4 benzene–petroleum ether. Solvent removal left 0.238 g. (45.3%) of white needles, m.p. 100°.

The infrared spectra of these three materials, as well as those of a sample prepared from styrene and 3,4-diphenyl-4-hydroxy-2-cyclopentenone[1] and a sample of the 119° form supplied by Dr. A. Halleux, were identical. The principal absorption bands in carbon tetrachloride solution were at 3040, 3010, 1940(w), 1875(w), 1800(w), 1750(w), 1670(w), 1600, 1575(w), 1490, 1472(s), 1440, 1385, 1177(w), 1072, 1027, 1008, 911, 895, 837, and 698(vs) cm.$^{-1}$ A supercooled melt showed, in addition, bands at 779, 756, and 742 cm.$^{-1}$ The ultraviolet spectrum in cyclohexane showed a minimum at 229 mμ (log ε 4.31), λ_{max} 248 mμ (log ε 4.54), an inflection at 270 mμ (log ε 4.39), and very low absorbance beyond 320 mμ.

Phenylacetylene trimer (?) The procedure of Rose and Statham[1] gave the 109° material in 1.4% yield; chromatographic purification of the residues, using the same procedure as used for 1,2,4-triphenylbenzene, provided an additional 7.1%. The infrared spectrum showed all of the bands of 1,2,4-triphenylbenzene at somewhat lower absorbance, except for a stronger 1490 cm.$^{-1}$; in addition, it absorbed strongly at 952 and 689 cm.$^{-1}$ and had weak bands at 1298, 1260, 1098, and 981(vw) cm.$^{-1}$ The ultraviolet spectrum in cyclohexane showed λ_{max} 248 mμ (log ε 4.40),[9] 280 mμ (log ε 4.32), and 335 mμ (log ε 3.90), with minima at 232 mμ (log ε 4.28), 266 mμ (log ε 4.30), and 333 mμ (log ε 3.89) and an inflection at 315 mμ (log ε 4.11).

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(5) All melting points are corrected. Infrared spectra were determined on a Perkin-Elmer Model 21 instrument with sodium chloride prism and ultraviolet spectra on a Carey Recording Spectrophotometer, Model 11.

(6) H. J. Backer, C. C. Bolt, and W. Stevens, *Rec. trav. chim.* **56**, 1063 (1937), modified by use of peroxyacetic acid in place of peroxybenzoic acid.

(7) W. M. Quattlebaum and C. A. Noffsinger, Brit. Pat. 615,521, Jan. 7, 1949.

(8) J. L. Melles and H. J. Backer, Rec. trav. chim., **72**, 319 (1953).

(9) Assuming molecular weight 306.

Pyrido[3,2-b][1,4]benzothiazine (1-Azaphenothiazine)

ALFONSO R. GENNARO[1]

Received February 16, 1959

Due to the importance of phenothiazine and its derivatives in medicinal chemistry it seemed of interest to synthesize the phenothiazine nucleus incorporating a nitrogen atom in one of the benzenoid rings. A recent publication by Yale and Sowinski[2] describes the preparation of 1-azaphenothiazine (I) by the Smiles rearrangement of 2′-(3-nitro-2-pyridylthio) acetanilide. Other 3- or 4-aza[3,4] and 4,6-diazaphenothiazines[5] are known. This paper is concerned with the direct thionation[6] of 2-anilinopyridine (II) to give I.

Heating II with sulfur in the presence of iodine catalyst affords a rapid method for obtaining I. Attempts to obtain I using other cyclization methods analogous to those reported for phenothiazine, such as: heating phenol and 2-aminopyridine with sulfur and iodine[7] or aluminum chloride; the thionation of II with aluminum chloride catalyst[8]; or directly with sulfuryl chloride[9] failed.

With picric acid I forms a *mono*picrate but a hydrochloride of definite composition could not be isolated. Oxidation of I with hydrogen peroxide in an attempt to form the 5-oxide or 5,5-dioxide regenerated II. Acylation with acetic anhydride gives the 10-acetyl derivative (III).

Preliminary attempts to alkylate I by the usual methods employed for phenothiazine (alkyl halide preceded by treatment with sodamide in a hydrocarbon solvent) were not successful. The only identifiable product obtained was II, which could arise by dethionation of I. Since dethionation of phenothiazine (with copper powder) leads to the formation of carbazole,[10] the product derived from I in such a case should be 9-pyrid[2,3-*b*]indole (α-carboline).[11] This compound was not identified in the reaction products of I with sodamide or copper. Raney nickel has been reported to remove the

(1) This study was initiated by a grant from the Institute for Muscle Research, New York, N.Y.

(2) H. L. Yale and F. Sowinski, *J. Am. Chem. Soc.*, **80**, 1651 (1958).

(3) T. Takahashi and E. Yoshi, *Pharm. Bull. (Tokyo)*, **2**, 382 (1954).

(4) (a) T. Takahashi and Y. Maki, *Yakugaku Zasshi*, **77**, 485 (1957); *Chem. Abstr.*, **51**, 14738a (1957). (b) V. A. Petrow and E. L. Rewald, *J. Chem. Soc.*, 591 (1945).

(5) Y. Maki, *Yakugaku Zasshi*, **77**, 862 (1957); *Chem. Abstr.*, **52**, 1174b (1958).

(6) A. Bernthsen, *Ann.* **230**, 73 (1885).

(7) Swiss patent **204,521**; *Chem. Abstr.*, **35**, 2338 (1941).

(8) F. Ackermann, D. R. P. **222,879**; *Chem. Abstr.*, **5**, 210 (1911).

(9) Kym, *Ber.*, **21**, 2807 (1888).

(10) A. Goske, *Ber.*, **20**, 232 (1887).

(11) R. Robinson, *J. Chem. Soc.*, 629 (1924).

sulfur of phenothiazine yielding the diarylamine.[12]

Subsequent attempts at alkylation of I using freshly prepared sodamide by the method of Yale did give the 10-alkyl derivative. Even in this instance some 2-anilinopyridine was recovered from the reaction mixture indicating partial reductive dethionation of I.

Thionation of *N*-phenyl-*N*-(2-pyridyl)-*N'*,*N'*-dimethyl ethylenediamine (IV), in an attempt to achieve ring closure with the 10-alkyl substituent (in this instance diethylaminoethyl) previously attached gave IV as the only isolable product.

As has been noted with phenothiazine, I changes color, developing a reddish crust on standing for a period of three years under normal conditions of light and temperature, with a subsequent lowering of the melting point. Recrystallization restores both color and melting point.

EXPERIMENTAL

Carbon and hydrogen analyses are by Clark Microanalytical Laboratory, Urbana, Ill. Nitrogen and sulfur analyses by Clark or this Laboratory. All melting points were determined using Anschutz, short scale thermometers, totally immersed in the heating bath.

1-Azaphenothiazine (I). A mixture of 12 g. (0.075 mole) of 2-anilinopyridine,[13] 4.8 g. of sulfur (0.15 g. atom) and 0.3 g. of iodine was intimately mixed in a mortar and heated under reflux at 160–180° (pot temperature) for 3 hr. The tarry mass was directly distilled from the reaction flask to give 6.3 g. (42%) of 1-azaphenothiazine (I), b.p. 178–184° at 3 mm., m.p. 109–112°. An analytical sample recrystallized from ethanol melted at 112.5–113.5° (yellow rosettes).

Anal. Calcd. for $C_{11}H_8N_2S$: N, 13.99; S, 16.00; Mol. wt. 200.3. Found: N, 14.07; S, 16.49, 16.20; Mol. wt. 196 (Rast). I gives the same color reactions used for the identification of phenothiazine.[14] A dilute alcoholic solution of I (0.05%) gives a green color with 1% aqueous ferric chloride and a red color with acidified hydrogen peroxide solution.

Reaction of I *with hydrochloric acid.* Mixing equimolar ethereal solutions of I and dry hydrogen chloride caused the precipitation of yellow crystals which, after recrystallization from absolute ethanol-ether, melted at 182–183° dec., and was only partially water soluble.

Anal. Calcd. for $C_{11}H_8N_2S.HCl$: Cl, 15.0; for $C_{11}H_8N_2S.2HCl$: Cl, 26.7. Found: Cl, 16.65.

With concentrated hydrochloric acid I formed a clear yellow solution and gave yellow needles on spontaneous evaporation. Two recrystallizations from absolute ethanol-ether gave yellow needles melting at 167–170°, which also showed incomplete water solubility and inconclusive analytical results.

Oxidation of I. Two grams of I (0.01 mole) in 50 cc. of ethanol at 50° was treated with 10 cc. (0.09 mole) of 30% hydrogen peroxide to give a clear yellow solution which on dilution with 5 volumes of water yielded 2-anilinopyridine, m.p. and mixed m.p. 109–110°.

Reaction of I *with copper.* Freshly precipitated copper was prepared by immersion of aluminum rods into a concentrated solution of copper sulfate with agitation. The precipitated copper was filtered, washed well with water, alcohol, and ether, then dried at 40° for 0.5 hr. and used immediately. An intimate mixture of 1 g. of I and 5 g. of copper powder was heated at 130° for 1 hr. in a nitrogen atmosphere. The powdered residue was extracted with ether, the solvent evaporated, and the pale yellow residue recrystallized from ethanol to give 0.27 g. of II, m.p. and mixed m.p. 108–110°.

1-Azaphenothiazine picrate. Mixing of saturated alcoholic solutions of I and picric acid gives the *mono picrate*, m.p. 198–200° dec.

Anal. Calcd. for $C_{17}H_{11}N_5O_7S$: N, 16.31. Found: N, 16.29.

Alkylation of I. Alkylation with dimethylaminoethyl chloride and sodamide[2] proceeded smoothly using freshly prepared sodamide. After vacuum distillation of the 10-alkyl derivative the residue in the flask solidified. Several recrystallizations from ethanol gave white plates, m.p. 108–109° which did not depress the melting point of an authentic sample of 2-anilinopyridine.

10-Acetyl-1-azaphenothiazine (III). A mixture of 2 g. (0.01 mole) of I, 0.21 g. (0.0025 mole) of anhydrous sodium acetate and 15 cc. of acetic anhydride (16.2 g., 0.16 mole) was refluxed for 0.5 hr. then poured into 50 cc. of ice water with stirring. Recrystallization of the separated solid from ethanol gave 2 g. (83.5%) of 10-acetyl-1-azaphenothiazine melting at 167–8° (pale yellow plates).

Anal. Calcd. for $C_{13}H_{10}N_2OS$: C, 64.43; H, 4.16; N, 11.55. Found: C, 64.53; H, 4.18; N, 11.28.

Infrared spectral data.[15] (KBr pellet, wave length and % transmission).

I[16]; 3.08 (23), 3.12 (36), 3.25 (38), 6.23 (20), 6.36 (33), 6.55 (29), 6.70 (12), 6.90 (1), 7.58 (28), 7.24 (33), 7.33 (41), 8.09 (67), 8.62 (72), 8.85 (41), 9.19 (50), 9.53 (26), 9.63 (58), 10.79 (62), 11.07 (67), 11.81 (63), 12.87 (12), 13.29 (8), 13.50 (1).

III; 3.27 (48), 5.89 (12), 6.30 (22), 6.36 (40), 6.75 (34), 7.01 (4), 7.25 (6), 7.58 (11), 7.64 (1), 7.76 (21), 7.93 (1), 8.27 (10), 8.72 (24), 8.84 (49); 9.19 (34), 9.55 (43), 9.69 (52), 9.87 (19), 10.04 (76), 10.60 (67), 10.18 (79), 11.05 (80), 11.62 (56), 12.45 (1), 13.00 (38), 13.15 (9), 13.30 (12), 13.40 (2), 13.69 (37), 14.20 (63).

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(12) K. H. Shah and K. Venkataraman, *Proc. Indian Acad. Sci.*, **28A**, 142 (1948).

(13) The preparation of substituted anilinopyridines and quinolines for the attempted synthesis of substituted 1-azaphenothiazines and azabenzophenothiazines by the thionation method has led to some interesting observations which will be discussed in a future paper.

(14) *The National Formulary*, 10th edition, J. B. Lippincott Co., Philadelphia, Pa. 1955, p. 442.

(15) The infrared spectra were run on a Beckman IR-4 double beam recording spectrophotometer equipped with sodium chloride optics.

(16) The infrared spectrum of I is identical with that of a sample of 1-azaphenothiazine generously supplied by Dr. H. L. Yale, The Squibb Institute for Medical Research, New Brunswick, N. J.

Preparation of 2-Imino- and 2-Nitrimino-1,3-diazacycloalkanes

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Received February 16, 1959

In a previous publication[1] the isolation of 5,5-bis(hydroxymethyl)-2-nitrimino-1,3-diazacyclohexane and the salts of 5,5-bis(hydroxymethyl)-

(1) L. S. Hafner and Robert Evans, *J. Am. Chem. Soc.*, 79, 3783 (1957).

2-imino-1,3-diazacyclohexane and 1-amino-2,2-bis-(hydroxymethyl)-3-guanidinopropane as three of the products of the reactions between 2-methyl-1-nitro-2-thiopseudourea or salts of 2-methyl-2-thiopseudourea and 1,3-diamino-2,2-bis(hydroxymethyl)propane has been described. The conditions for these reactions have been extended and modified so that the reaction of alkyldiamines with the salts of 2-methyl-2-thiopseudourea or with 2-methyl-1-nitro-2-thiopseudourea can be considered as a general method of preparation for 2-nitrimino-1,3-diazacycloheptanes, hexanes, and pentanes as well as for 2-imino-1,3-diazacyclohexanes and pentanes. In Table I the yields of 2-nitrimino-1,3-diazacycloalkanes obtained from the reaction between the corresponding diamine and 2-methyl-1-nitro-2-thiopseudourea are compared with those obtained by McKay and Wright[2] from the reaction between alkyldiamines and nitroguanidine. When 1,3-diaminopropanol was allowed to react with 2-methyl-1-nitro-2-thiopseudourea, the amounts of the products formed were dependent on the reaction medium. In water the yield of 5-hydroxy-2-nitrimino-1,3-diazacyclohexane was 46%, the yield of 2-imino-1,3-diazacyclohexane 20%, and 17% unreacted 1,3-diaminopropanol was recovered. With ethanol as the reaction medium, the yield of the imino compound was 38%, of the nitrimino compound 15%, while 34% unreacted 1,3-diaminopropanol was recovered.

TABLE I

2-NITRIMINO-1,3-DIAZACYCLOALKANES

Compound	M.P.	Yield, %	Lit.[a] M.P.	Lit.[a] Yield
2-Nitrimino-1,3-diazacyclopentane	215–218 dec.	72.1	220–221 dec.	65.4
4-Methyl-2-nitrimino-1,3-diazacyclopentane	170–173	64.3	170.5	64.0
5-Hydroxy-2-nitrimino-1,3-diazacyclohexane	228–235	50.5	233–235	59.0
2-Nitrimino-1,3-diazacyclohexane	255–256 dec.	36.4	251–252 dec.	55.0
2-Nitrimino-1,3-diazacycloheptane	226–227 dec.	14.5	219–220 dec.	64.3

[a] A. F. McKay and G. F. Wright, *J. Am. Chem. Soc.*, **70**, 430 (1948).

In order to determine whether or not the imino compound could be formed in the reaction between nitroguanidine and an alkyldiamine,[2] an excess of the dihydrochloride salt of 1,3-diaminopropanol was reacted with an aqueous solution of nitroguanidine (10% excess) and potassium hydroxide. A 12% yield of the imino compound was isolated as the picrate.

There is some indication[1] that when 2-methyl-2-thiopseudourea salts are reacted with alkyldiamines, 1-amino-3-guanidinoalkane may be an intermediate in the formation of 2-imino-1,3-diazacycloalkanes. In order to test this theory, 1-amino-3-guanidinopropanol was prepared as the dihydrochloride salt. This salt, when half neutralized with aqueous sodium hydroxide and heated, gave a 53% yield of the hydrochloride salt of 5-hydroxy-2-imino-1,3-diazacyclohexane. Apparently the salt of 2-methyl-2-thiopseudourea reacts first with one amino group of the alkyldiamine to form the salt of 1-amino-3-guanidinoalkane; then if the reaction conditions are favorable for cyclization, ammonia is eliminated and the cyclic compound is formed instead of the 1,3-bis-(guanidino)alkane salt. Table II lists the yields of 2-imino-1,3-diazacycloalkanes, isolated as the picrates, prepared by the reaction between the nitrate salt of 2-methyl-2-thiopseudourea and the corresponding alkyldiamine.

TABLE II

2-IMINO-1,3-DIAZACYCLOALKANES

Picrate	Yield, %	M.P.	M.P.
2-Imino-4-methyl-1,3-diazacyclopentane[a]	65.2	195–196	—
2-Imino-1,3-diazacyclohexane[b]	57.2	185–186	—
5-Hydroxy-2-imino-1,3-diazacyclohexane[c]	62.5	184–186	—
2-Imino-1,3-diazacyclopentane[d]	57.0	223–224	218–220

[a] Calcd. for $C_{10}H_{12}N_6O_7$: C, 36.58; H, 3.69; N, 25.60. Found: C, 37.03; H, 3.86; N, 25.75. [b] Calcd. for $C_{10}H_{12}N_6O_7$: C, 36.58; H, 3.69; N, 25.60. Found: C, 36.77; H, 3.69; N, 25.30. [c] Calcd. for $C_{10}H_{12}N_6O_8$: C, 34.88; H, 3.51; N, 24.41. Found: C, 34.93; H, 3.99; N, 24.44. [d] O. Stefanye and W. Howard, *J. Am. Chem. Soc.*, **77**, 761 (1955).

During this investigation 1-amino-3-guanidinopropane was nitrated to give what was probably 1-amino-3-nitroguanidinopropane which was isolated as the picrate and nitrate salts.

EXPERIMENTAL[3,4]

2-Nitrimino-1,3-diazacycloalkanes (Table I). The diamine (0.05 mole) in 30 ml. of water was placed in a flask and heated to 55° with stirring while 0.0525 mole of 2-methyl-1-nitro-2-thiopseudourea was added in increments over a period of 15 min. The reaction mixture was heated for an additional 30 min. at the same temperature, then cooled, and filtered. The precipitate was washed with cold water and crystallized from hot water.

Reaction of nitroguanidine with 1,3-diaminopropanol. Potassium hydroxide (6.24 g. of 85.3%, 0.095 mole) dissolved in 17 ml. of water was placed in a flask fitted with a stirrer. Nitroguanidine (5.77 g., 0.055 mole) was added and stirred until solution was complete. 1,3-Diaminopropanol dihydrochloride (9.05 g., 0.055 mole) was then added and the mixture stirred and warmed to 60–65° for 30 min. At the end of the reaction period the mixture was cooled in an ice bath and filtered. The precipitate was washed with

(2) A. F. McKay and G. F. Wright, *J. Am. Chem. Soc.*, **70**, 430 (1948).

(3) All melting points were measured on a Kofler micro hot stage.

(4) The yields are based on the total amount of diamine.

ethanol, and this ethanol wash was combined with the original reaction filtrate. An ethanol solution of picric acid was added to these combined solutions and two crystalline picrates were obtained. The first picrate, weighing 12.9 g., was removed and upon examination proved to be a mixture of potassium picrate and the dipicrate of 1,3-diaminopropanol. The second picrate, which weighed 3.16 g., was extracted with ether to remove residual picric acid and recrystallized from ethanol. Three crops were obtained. The second and third crops were combined and recrystallized from ethanol; care was taken not to dissolve all the solid in the ethanol (about 0.2 g.). A picrate was obtained which melted at 179–185° (2.0 g., 10.5% calculated as 5-hydroxy-2-imino-1,3-diazacyclohexane picrate). After recrystallization from ethanol the compound melted at 182–185°. A mixed melting point with an authentic sample of 5-hydroxy-2-imino-1,3-diazacyclohexane picrate was not depressed. The combined first crops and insolubles were processed and an additional 1.5% of the imino compound was isolated.

1-Amino-3-guanidinopropanol dihydrochloride. 1,3-Diaminopropanol (25.1 g., 0.278 mole) was dissolved in 35 ml. of ethanol, heated to 40° and stirred while 56.2 g. (0.368 mole, 32% excess) of 2-methyl-2-thiopseudourea nitrate dissolved in 35 ml. of warm water was added over a period of 40 min. After the addition was complete, the reaction mixture was maintained at 40° for an additional 15 min., then cooled, filtered, and the precipitate washed with ethanol. The filtrate was added to an excess of an aqueous picric acid solution and the picrate formed, after extraction with ether and hot methanol, weighed 39.0 g. These salts, after conversion to hydrochloride salts, weighed 10.2 g. (17.9%) and melted at 145–150°. Recrystallization from ethanol gave a product which melted at 154.5–155.5°.

Anal. Calcd. for $C_4H_{14}Cl_2N_4O$: C, 23.42; H, 6.88; Cl, 34.58; N, 27.32. Found: C, 23.42; H, 6.55; Cl, 34.28; N, 27.37.

1-Amino-3-guanidinopropane dihydrochloride. This salt was prepared in the same manner as 1-amino-3-guanidinopropanol. However, a somewhat smaller excess of 2-methyl-2-thiopseudourea nitrate can be used since the dihydrochloride salt of 1,3-diaminopropane separates readily from the dihydrochloride salt of 1-amino-3-guanidinopropane when the hydrochloric acid solution is allowed to evaporate. After crystallization from absolute ethanol and then from an ethanol-benzene solution, the product melted at 156–157°.

Anal. Calcd. for $C_4H_{14}Cl_2N_4$: C, 25.41; H, 7.46; Cl, 37.50; N, 29.63. Found: C, 25.41; H, 7.68; Cl, 37.90; N, 29.69.

Cyclization of 1-amino-3-guanidinopropanol. A. 1-Amino-3-guanidinopropanol dihydrochloride (0.3 g., 0.00146 mole) was added to 15 ml. of water and refluxed 3 hr. An excess of an aqueous picric acid solution was then added, and the precipitate which formed was collected and extracted with ether. A mixed melting point with an authentic sample of 1-amino-3-guanidinopropanol dipicrate was not depressed.

B. 1-Amino-3-guanidinopropanol dihydrochloride (0.28 g., 0.00139 mole) was added to 15 ml. of water containing 0.00138 mole of sodium hydroxide and refluxed for 2 hr. An excess of an aqueous solution of picric acid was added, and the precipitate after extraction with ether melted at 185–186° and weighed 0.25 g. (52%). A mixed melting point with an authentic sample of 5-hydroxy-2-imino-1,3-diazacyclohexane picrate was not depressed.

2-Imino-1,3-diazacycloalkane salts. The corresponding diamine (0.04 mole) was dissolved in 10 ml. of water in a flask equipped with a reflux condenser and stirrer. The diamine solution was heated to reflux and 0.04 mole of the nitrate salt of 2-methyl-2-thiopseudourea, dissolved in 25 ml. of water, was added over a period of 40 min. After the addition was complete, the reaction mixture was refluxed for 3 hr. The water was then removed under aspirator pressure (30 mm.). The residue was dissolved in ethanol, added to an excess of picric acid dissolved in water, and allowed to stand overnight. The precipitate was removed and purified by crystallization from ethanol. Pertinent data about the picrates formed are given in Table II. Two of the picrates formed were converted to nitrate salts:

(a) 2-Imino-1,3-diazacyclopentane nitrate salt. This compound melted at 112.5–114.0°.

Anal. Calcd. for $C_3H_8N_4O_3$: C, 24.32; H, 5.44; N, 37.83. Found: C, 24.24; H, 5.40; N, 37.57.

(b) 2-Imino-1,3-diazacyclohexane nitrate salt. This compound melted at 160–161°.

Anal. Calcd. for $C_4H_{10}N_4O_3$: C, 29.63; H, 6.22; N, 34.55; Found: C, 29.54; H, 6.38; N, 34.29.

Nitration of 1-amino-3-guanidinopropane. 1-Amino-3-guanidinopropane dihydrochloride (2.0 g.) was added with cooling to 7 ml. of concentrated sulfuric acid. After all the salt had dissolved and the evolution of hydrogen chloride was complete, the solution was cooled to −30° and 4 ml. of 99% nitric acid was added. The nitration mixture was allowed to reach room temperature and held for 1 hr. The mixture was then poured over crushed ice and treated with a barium hydroxide solution until just acid to congo red paper. The barium sulfate was removed and the filtrate evaporated in a current of air. Barium nitrate crystallized and was removed as the solution was concentrated. The final residue weighed 2.08 g. (87%) and melted at 130–138°. After recrystallization from an ethanol-water solution, the salt melted at 140–141°. Considering the conditions used for nitration, this compound was probably the nitrate salt of 1-amino-3-nitroguanidinopropane. The ultraviolet absorption spectrum showed a maximum at 269–270 mμ which corresponded to a maximum obtained by McKay and Sandorfy[5] for the nitroguanidino group.

Anal. Calcd. for $C_4H_{12}N_6O_5$: C, 21.43; H, 5.39; N, 37.49. Found: C, 21.83; H, 5.62; N, 37.08.

The *nitrate* salt was converted to the picrate which melted at 190–192°.

Anal. Calcd. for $C_{10}H_{14}N_8O_9$: C, 30.77; H, 3.61; N, 28.71. Found: C, 30.99; H, 3.38; N, 28.90.

Acknowledgment. We wish to thank Mrs. P. P. Wheeler and Mrs. Kathleen Rumbaugh for the microanalyses and Mr. Robert H. Philp, Jr., for technical assistance.

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(5) A. F. McKay and C. Sandorfy, *Can. J. Chem.*, **31**, 42 (1952).

Inhibition of the Nitrostyrene Condensation in Acetic Acid by Traces of Water[1]

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Received February 19, 1959

Catalysis by a primary amine in glacial acetic acid is frequently prescribed for the synthesis of β-nitrostyrenes from aromatic aldehydes and nitromethane.[2] In extending our earlier studies of

(1) This work was supported by the Office of Ordnance Research, U. S. Army, and by the National Science Foundation. The kinetic studies are from the M.S. thesis of Charles E. Bell, Jr., University of Virginia, 1955.

(2) W. S. Emerson, *Chem. Revs.*, **45**, 347 (1949).

nitrostyrene formation[3,4] to these conditions, we noticed a striking effect of water, in low concentrations, upon the rate. A mechanistic interpretation of these observations is given in this paper.

The reaction of piperonal with nitromethane at 100.4° follows a second-order course at a given *n*-butylamine concentration. The rate constant, k_2, is proportional to the *n*-butylamine concentration, indicating third-order (pseudo second-order) kinetics. Figure 1 shows the dependence of k_2 on the water concentration.

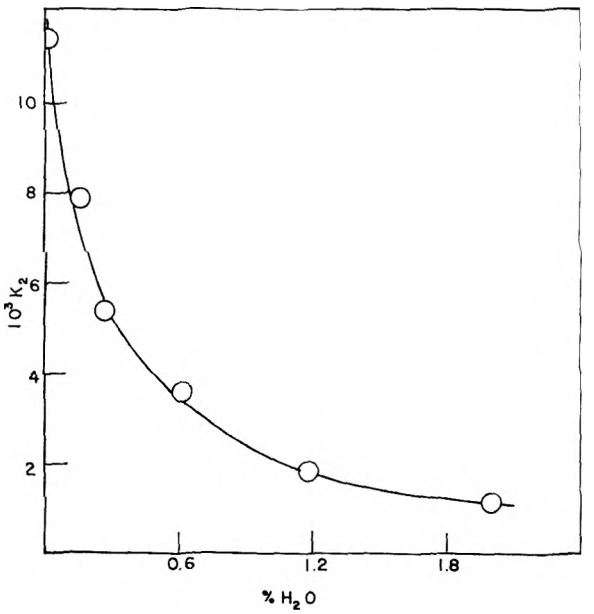

Fig. 1. Rate of nitrostyrene formation as a function of weight percent water in the solvent

Kolthoff and Bruckenstein[5] have made a careful study of the species present in acetic acid solutions of water and other bases. Before attempting a thorough kinetic investigation of acid-base catalysis of the reaction in so complex a mixture, we have simply correlated the observed effect of water with a reversal of the first step of the mechanism previously proposed, involving piperonylidene *n*-butylamine as intermediate.[4]

$$ArCHO + BuNH_2 \rightleftharpoons ArCH{=}NBu + H_2O \quad (1)$$

$$ArCH{=}NBu + CH_3NO_2 \rightarrow ArCH{=}CHNO_2 + BuNH_2 \quad (2)$$

The concentration of this Schiff base is easily measured spectrophotometrically, in the absence of nitrostyrene, and the equilibrium constant for equation 1 calculated. The expression $K = (ArCH{=}NBu)(H_2O)/(ArCHO)(BuNH_2)$ apparently holds for stoichiometric concentrations, even though *n*-butylamine, water and the Schiff base must exist predominantly as their conjugate acids in acetic acid. The value of K at 100.4° is 0.18, the mean of sixteen measurements over a fifteen- to fifty-fold range in concentration of each of the reactants. Although the results are not very precise (the average deviation from the mean is 0.06) they serve to establish the fact that in the range of concentrations encountered in the kinetic studies, the extent of reaction of aldehyde with amine, to form Schiff base, cannot be neglected, and is given by the constant K.

At 25°, $K = 0.37$, which is smaller than in methanol[6] by a factor of nearly 10^4, possibly because the more complete ionization of *n*-butylamine, the strongest base present, shifts the equilibrium 1 to the left in acetic acid. In methanol, none of the species is appreciably ionized.

The initial concentration of Schiff base in any reaction mixture can now be calculated from K and the initial concentrations of *n*-butylamine, piperonal,[7] and water, for step 1 is comparatively

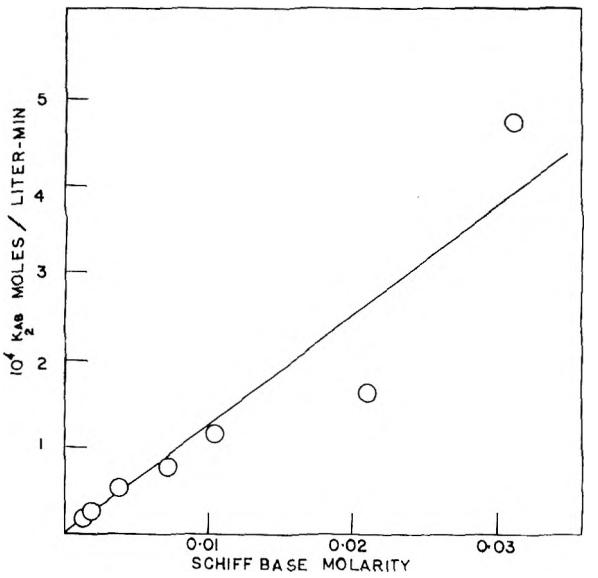

Fig. 2. Rate of nitrostyrene formation as a function of calculated Schiff base concentration

(3) T. I. Crowell and F. A. Ramirez, *J. Am. Chem. Soc.*, **73**, 2268 (1951).

(4) T. I. Crowell and D. W. Peck, *J. Am. Chem. Soc.*, **75**, 1075 (1953).

(5) I. M. Kolthoff and S. Bruckenstein, *J. Am. Chem. Soc.*, **78**, 1, 10 (1956).

(6) R. L. Hill, and T. I. Crowell, *J. Am. Chem. Soc.*, **78**, 2284, 6425 (1956).

(7) In one experiment, Schiff base was substituted for piperonal. The deviation of the point at 0.021*M* Schiff base in Fig. 2 could result from an increment of 0.02% in the water content of the solvent, which corresponds to the amount of water later found to be introduced with the *n*-butylamine. The lower points, obtained with the same sample of *n*-butylamine, are less sensitive to extraneous traces of water.

However, the water content of the *n*-butylamine used in the experiment starting with Schiff base (the point at 0.031*M*) was known and in this case incorporated into the calculation.

rapid and step 2 rate-controlling. Figure 2 shows the initial rate, k_2ab, plotted against this calculated Schiff base concentration. The straight line obtained indicates second-order kinetics involving the Schiff base and nitromethane concentrations, consistent with a mechanism in which the Schiff base or its conjugate acid is an intermediate.

As we stated earlier,[3] the existence of a Schiff base intermediate does not preclude catalysis by secondary and tertiary amines. Preliminary experiments led to the isolation of nitrostyrene when piperidine and triethylamine were substituted for *n*-butylamine. A 74% yield was obtained with *N*-butylacetamide, in analogy with the efficiency of acetamide as catalyst for condensations in acetic acid.[8] It is quite possible that piperonylidene *n*-butylamine was formed under these conditions.[9]

EXPERIMENTAL

Materials. Glacial acetic acid, reagent grade, was dried by adding either acetic anhydride or benzene and fractionating. The water content was found by Karl Fisher titration to be 0.03%. Other reagents were as previously described.[4]

Formation of piperonylidene *n*-butylamine in acetic acid was demonstrated by its preparation in 74% yield.

Kinetic studies. Piperonal (about 0.2 g.) was weighed into a volumetric flask and dissolved in acetic acid. Nitromethane, *n*-butylamine, and water were added with calibrated pipets before dilution to 50 ml. This solution was then divided into 5-ml. samples which were sealed in 12 mm. diameter Pyrex ampoules and immersed for the desired time in a polyethylene glycol bath at 100.4 ± 0.3°. The ampoules were removed at intervals, cooled, and opened, and the contents transferred quantitatively into a solution of 2,4-dinitrophenylhydrazine for gravimetric determination of the aldehyde.[3]

Equilibrium studies. A solution of *n*-butylamine, water, and piperonylidene *n*-butylamine or piperonal was prepared in a drybox and placed in the thermostat. Equilibrium was reached within a minute or two. A sample was withdrawn after 30 min. and pipetted into methanolic hydrochloric acid for spectrophotometric determination of the Schiff base conjugate acid.[4] The rather small temperature coefficient of K probably rendered any shift of equilibrium, due to cooling of the sample during transfer, unimportant in this work. Since this sample was the only volume measured at 100°, the resulting Schiff base concentration was multiplied by 1.08, the ratio d_{25}/d_{100} for acetic acid. Thus, the concentrations given in this paper refer to solutions at 25°. While K would be independent of concentration units, the rate constant, k_2, must be multiplied by 1.08 for conversion to l/mole min. at the reaction temperature.

The spectrum of the methanol dilution of the reaction mixture showed only the peaks of piperonal and Schiff base in concentrations equal in sum to the stoichiometric piperonal concentration.

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(8) A. C. Cope, *J. Am. Chem. Soc.*, **59**, 2327 (1937).

(9) R. N. Castle, *J. Am. Pharm. Assoc.*, **40**, 162 (1951), reports the formation of Schiff bases from aldehydes and sulfonamides in acetic acid.

New Synthesis of Dimethylaminodimethylborane

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Received February 19, 1959

In the course of preparing dimethylaminomethylchloroborane, $(CH_3)_2NB(CH_3)Cl$,[2] moderate amounts of dimethylaminodimethylborane, $(CH_3)_2NB(CH_3)_2$, were required. Previous syntheses of the latter compound[3-5] were conducted in vacuum trains, under conditions not easily attained in ordinary laboratory equipment.

We have found that $(CH_3)_2NB(CH_3)_2$ may be prepared in high yield and in reasonable quantity by the action of methyl Grignard reagent on dimethylaminodichloroborane, $(CH_3)_2NBCl_2$. This is the first direct application of a Grignard reagent to the synthesis of an aminodialkylborane. Similar applications to the synthesis of *B*-alkylborazines (*i.e.*, *B*-alkylborazoles) have recently been discussed.[6-8]

We believe that this reaction represents a general method for the synthesis of dialkyl (and, presumably, diaryl) boron compounds that have been prepared up to now only by more indirect or cumbersome methods. The dimethylamino group may be regarded as a blocking group and can subsequently be replaced if desired. For example, hydrolysis yields a dialkylhydroxyborane (i.e., borinic acid).

EXPERIMENTAL

The reaction is carried out in a three-neck flask, fitted with a dropping funnel and stirrer, and protected with a dry nitrogen atmosphere. Dimethylaminodichloroborane, diluted with 10 to 20 volumes of ether, is placed in the flask, which is then immersed in an ice bath. The theoretical amount of methyl Grignard reagent in ether is added dropwise over a 3-hr. period, after which the bath is removed. The stirring is continued until the solution and suspended magnesium salts have warmed to room temperature. The ether and the product are then distilled from the flask at reduced pressure, trapping them in a reservoir at Dry Ice temperature. The residual magnesium salts are heated briefly to insure complete separation of product. Subsequent fractional distillation of the ether solution yields a small forerun and a main fraction of $(CH_3)_2NB(CH_3)_2$, boiling at 63–65° at atmospheric pressure. The product of an early run was found to contain 16.2%*N* (theory, 16.5%) by a Kjeldahl procedure. The chlorine content was nil. Methanol gave an adduct, melting at 49–51° (lit. 51–53°).[4]

(1) Present address: Esso Research and Engineering Co., Linden, N. J.

(2) To be published subsequently.

(3) E. Wiberg, *Naturwiss.*, **35**, 182 and 212 (1948).

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Three runs gave yields of 49–61% of isolated, pure product in amounts up to 5.5 g. When product in the forerun and still residue was included, the yield was 69–71%. One run that gave a yield of only 20% was carried out with the flask initially immersed in a Dry Ice bath. When this was done the Grignard reagent did not react until after all of it had been added and the flask was warmed to near room temperature. A large amount of trimethylborane was formed, resulting in a low yield of the desired product. When the reaction was conducted at 0°, an excess of Grignard reagent was avoided, and yields were very good. Dimethylaminodibromoborane reacted equally well.

Dimethylaminodiethylborane was also prepared[9] in 58% yield of distilled, pure product from dimethylaminodibromoborane and an ethyl Grignard reagent.

Acknowledgement. The authors gratefully acknowledge a Frederick Gardner Cottrell Grant awarded by the Research Corp. in support of this research.

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Some Reactions of Methyl 2,4,6-Heptatrienoate

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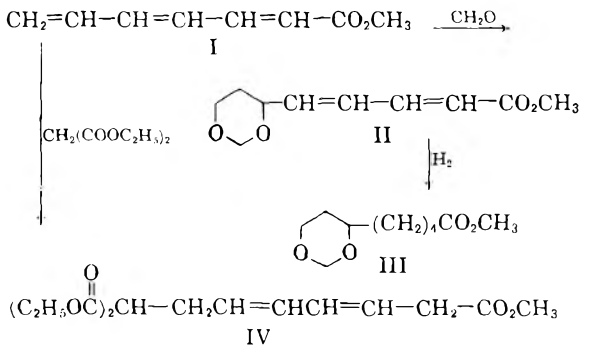
Received February 20, 1959

Previous work[1,2] with long conjugated systems has indicated that most reactions yield mixtures of products which are quite difficult to separate. However, we have found that methyl 2,4,6-heptatrienoate[2] (I) reacts with surprising selectivity with formaldehyde in an acid-catalyzed reaction and with diethyl malonate in a base-catalyzed reaction. The products in each case result from attack of the reactive species on the terminal portion of the long conjugated system. There have been few, if any, examples in the literature of this type of selective reaction.

Condensation of methyl 2,4,6-heptatrienoate (I) with formaldehyde in dioxane-sulfuric acid gave methyl 6,8-methylenedioxy-2,4-octadienoate (II) in 35% yield. The structure of II was determined by its ultraviolet spectrum and by hydrogenation to methyl 6,8-methylenedioxyoctanoate (III), a known compound.[3]

The saturated ester III was obtained from I in 48% over-all yield when the ester II was hydrogenated without purification. The identity of III



was further established by its conversion to lipoic acid by a series of known reactions.[3,4]

The base-catalyzed (Michael) addition of diethyl malonate to Compound I occurred predominantly in a 1,8-manner as shown by conversion of methyl 2,4,6-heptatrienoate through the intermediate diolefinic triester (IV) to azelaic acid in 62% yield. The high yield of azelaic acid is remarkable in view of the number of possible side reactions.

EXPERIMENTAL

Azelaic acid. A solution of 0.6 g. of sodium in 6 ml. of absolute methanol was diluted with 10 ml. of dry ether and then mixed with a solution of 20 g. (0.145 mole) of freshly distilled methyl 2,4,6-heptatrienoate in 75 ml. of diethyl malonate. The resulting solution was heated under reflux on a steam bath for 21 hr. and then diluted with 400 ml. of ether. This was washed with 12 ml. of 2*N* hydrochloric acid and two 10-ml. portions of water. The ethereal solution was dried over anhydrous magnesium sulfate, and all material volatile at 0.2 mm. at steam bath temperature was removed. The residual oil was dissolved in 100 ml. of absolute ethanol and hydrogenated in a low pressure apparatus over 10% Pd on carbon. The hydrogen absorption was rapid and stopped sharply. The catalyst was removed and the mother liquor diluted with 200 ml. of 95% ethyl alcohol before 40 g. of potassium hydroxide was added. This mixture was heated under reflux for 2 hr. Water (300 ml.) was then added and the apparatus was arranged for distillation. After all of the alcohol and 100 ml. of water had distilled, the mixture was cooled and carefully treated with 200 ml. of concentrated hydrochloric acid. After refluxing 40 hours, the solution was evaporated to dryness and extracted with ether. The ether was concentrated to give 16.0 g. of crude azelaic acid, m.p. 97–103°. This was recrystallized from water with 85% recovery to give good quality azelaic acid, m.p. 104–106°, which did not depress the melting point of an authentic sample. Infrared comparison confirmed its identity. The ether solution was evaporated to dryness to give an oil which upon distillation yielded (after recrystallization) 0.92 g. of azelaic acid, m.p. 103–107° (total yield 16.92 g., 62%) and 3.5 g. of material distilling at 100–125° (0.2 mm.) which was not identified.

Methyl 6,8-methylenedioxy-2,4-octadienoate (II). A mixture of 55 g. of purified dioxane, 8.0 g. of 96% sulfuric acid, and 6.0 g. (0.20 mole) of paraformaldehyde was stirred briefly and cooled to 0°. Methyl 2,4,6-heptatrienoate, 13.8 g. (0.10 mole), was added slowly, and the mixture was stirred at room temperature for 40 hr. The reaction mixture was cooled in an ice bath and diluted with 300 ml. of ice water. The organic layer was separated, and the water was extracted with three 150-ml. portions of ether. The organic layer and

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the ether extracts were combined and dried with magnesium sulfate, and the ether was distilled. The residue was distilled through a 4-in. Vigreux column to give 4.5 g. (23%) of methyl 6,8-methylenedioxy-2,4-octadienoate, b.p. 108–115° (0.7 mm.), n_D^{25} 1.5180, λ_{max} 257 mμ, ε 23,000.

Anal. Calcd. for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.14; H, 7.34.

A repetition of this experiment using 55.2 g. (0.40 mole) of methyl heptatrienoate afforded 27.4 g. (34.6%) of methyl 6,8-methylenedioxy-2,4-octadienoate, b.p. 95–124° (0.15 mm.), n_D^{25} 1.5178–1.5200.

Methyl 6,8-methylenedioxyoctanoate. A mixture of 4.31 g. (0.0218 mole) of methyl 6,8-methylenedioxy-2,4-octadienoate, 0.5 g. of 10% palladium-on-carbon, and 100 ml. of hexane was placed in a pressure bottle and hydrogenated in a Parr shaker until hydrogenation was complete. The uptake was 112% of the theoretical amount. The solution was filtered to remove the catalyst, and the solvent was distilled. The residue was fractionated in a 4-in. Vigreux column. There was obtained 3.81 g. (87%) of methyl 6,8-methylenedioxyoctanoate, b.p. 78° (0.1 mm.), n_D^{25} 1.4508–1.4518. The *n-m-r* spectrum was consistent with the structure assigned and was confirmed by comparison with *m*-dioxane and methyl valerate references.

Anal. Calcd. for $C_{10}H_{18}O_4$: C, 59.41; H, 8.91. Found: C, 59.24; H, 9.00.

The constants listed for this compound[3] are b.p., 112° (0.01 mm.) and n_D^{22}, 1.4519.

Methyl 6,8-Methylenedioxyoctanoate (direct procedure). A mixture of 19.5 g. (0.65 mole) of paraformaldehyde, 150 ml. of dioxane, and 25 g. of concentrated sulfuric acid was cooled to 0°, and 44.0 g. (0.318 mole) of methyl 2,4,6-heptatrienoate was added. The mixture was stirred at room temperature for 42 hr. and diluted with 300 ml. of ice water. The organic layer was separated, and the water layer was extracted with three 150-ml. portions of ether. The organic layers were combined and dried with magnesium sulfate. The ether was distilled, and the residue was diluted to a volume of 250 ml. with 50% methanol-cyclohexane and hydrogenated using 110 g. of 10% palladium-on-carbon catalyst. Distillation of the product afforded 30.7 g. (48%) of methyl 6,8-methylenedioxyoctanoate, b.p. 94.5° (0.47 mm.) to 102° (0.27 mm.), n_D^{25} 1.4489–1.4498.

Acknowledgment. We are indebted to Dr. G. H. Kalb of this department for the methyl heptatrienoate.

CONTRIBUTION NO. 529
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New Route to Carbon-14 Labeled *N*-(1-Hydroxy-2-fluorenyl)acetamide[1]

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Received February 20, 1959

The binding of chemical carcinogens or metabolites thereof to cellular proteins is thought to be causally related to the induction of neoplasms.[2] In the case of the carcinogen *N*-2-fluorenylacetamide it has been shown that hydroxylation was required for binding of the compound.[3] Based on this observation the theory has been advanced that the hydroxylated metabolites are further oxidized to quinone imides or imines and that these reactive metabolites combine with proteins.[4] Recently, evidence has been provided that 2-amino-1-fluorenol was oxidized, either by mitochondria and cytochrome c or by cytochrome oxidase and cytochrome c, to the *o*-quinone imine, 1,2-fluorenoquinone-2-imine. In the presence of crystalline bovine serum albumin this oxidation product added rapidly to the protein.[5]

We desired to determine the mechanism of the oxidation of 2-amino-1-fluorenol as well as the site and extent of binding of the oxidation product in the intact cell under physiological conditions. For this purpose, we required 2-amino-1-fluorenol and *N*-(1-hydroxy-2-fluorenyl)acetamide labeled with carbon-14 in the fluorene nucleus. The fluorene system has been shown to be resistant to metabolic attack.[6]

The available chemical synthesis of these compounds[7,8] from fluoranthene does not permit the incorporation of carbon-14 into the molecule. Carbon-14 labeled *N*-(1-hydroxy-2-fluorenyl)-acetamide has been made biosynthetically by feeding *N*-(2-fluorenyl-9-C^{14})acetamide to rats and isolating *N*-(1-hydroxy-2-fluorenyl-9-C^{14})acetamide from the urine, the label here being situated in the stable 9 position.[9] The drawback to this method is that it requires the chromatographic separation of the desired *N*-(1-hydroxy-2-fluorenyl-9-C^{14})acetamide from other labeled hydroxylated metabolites and the careful purification of the isolated material by carrier methods. *N*-(1-hydroxy-2 fluorenyl)acetamide is only a minor urinary metabolite[10] and the method of isolation necessitates further dilution of the label which places limitations on the specific radioactivity of the final product. For these reasons it appeared desirable to work out an alternative route for the chemical synthesis of carbon-14 labeled *N*-(1-hydroxy-2-fluorenyl)acetamide.

A new approach became possible with the development of a synthesis of 1,2,3,4-tetrahydro-

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fluoren-1-one from indene.[11] The treatment of 3-(3′-indenyl)propyl bromide[11] with potassium cyanide-C^{14} gave 4-(3′-indenyl)butyronitrile-1-C^{14}. Cyclization of the nitrile and hydrolysis to the labeled tetrahydrofluorenone was accomplished by an adaptation of the method of Howell and Taylor[11] to the semimicro scale. A variety of catalysts, solvents, and reaction times were investigated in attempts to effect the dehydrogenation of the ketone to 1-fluorenol. In each case the ketone and catalyst were heated at the reflux temperature of the solvent for periods of 10 minutes to 24 hours. No detectable 1-fluorenol was formed with the use of palladium black in *m*-xylene or naphthalene, with 10% palladium-on-charcoal in *p*-cymene or naphthalene, or with chloranil in *m*-xylene. With fluorene as solvent, 10% palladium-on-charcoal gave a maximum yield of 30% 1-fluorenol. The optimum conditions, however, were found using palladium black as catalyst, fluorene as solvent, and a reaction time of 4–5 hours. Crude yields of 65% of 1-fluorenol-1-C^{14} were realized under these conditions. Nitration of 1-fluorenol-1-C^{14} gave 2-nitro-1-fluorenol-1-C^{14}.[8] Reduction by zinc dust, calcium chloride, and ethanol[12] converted the nitrofluorenol to 2-amino-1-fluorenol-1-C^{14}. Acetylation was carried out in the usual manner.[13] The overall radioactive yield of *N*-(1-hydroxy-2-fluorenyl-1-C^{14})acetamide was 5.1%, and the final product had a specific radioactivity of 0.66 mC./mM.

This synthetic route to the formation of 2-amino-1-fluorenol and its acetamide, in addition to being the only feasible method at present for incorporation of radioactive carbon in the fluorene nucleus, has been used successfully for large scale preparations of the unlabeled compounds. The overall yield is comparable to that which can be obtained by the method using fluoranthene as starting material,[7,8] but the reaction sequence is shorter by one step.

During the large scale preparation of 1,2,3,4-tetrahydrofluoren-1-one it was found that more extensive purification of the intermediate 4-(3′-indenyl)butyronitrile resulted in crystallization of this material which had previously been reported as an impure liquid.[11] This compound has now been more fully characterized.

EXPERIMENTAL

Melting points were determined on a Fisher-Johns melting point block and are uncorrected as are boiling points. Radioactivity measurements were made by the micro method previously described.[14]

4-(3′-Indenyl)butyronitrile-C^{14}. A solution of 1.28 g. (5.4 mmoles) of 3-(3′-indenyl)propyl bromide[11] in 0.9 ml. of absolute ethanol was placed in a 10 ml. pear-shaped flask. Potassium cyanide-C^{14} (0.163 g., 2.51 mmoles)[15] and sodium cyanide (0.170 g., 3.47 mmoles) were added, followed by 0.4 ml. of water. The reaction flask was fitted with a reflux condenser carrying at the top a glass tube which led into a 10% potassium hydroxide solution. This trapping arrangement was necessary to prevent the escape of small quantities of hydrogen cyanide-C^{14} during the reaction. The solution was then heated under reflux for 9.5 hr. The mixture was allowed to stand at room temperature overnight and was then treated with 2 ml. of 10% potassium hydroxide solution. Without delay the solution was extracted with 3-ml. portions of ether until the extract was colorless, about 5 portions being required. The ether extracts were combined in a 50-ml. dropping funnel which contained some anhydrous sodium sulfate supported on glass wool, and the solution was percolated through a column (1 × 14 cm.) of acid-washed, activated alumina using a total volume of 40–50 ml. of ether. With the small quantities of compound used in the radioactive run purification by column chromatography was more practical than the vacuum distillation recommended by Howell and Taylor.[11] The solvent was evaporated by means of an infrared lamp. Vapors of ether and hydrogen cyanide-C^{14} were trapped by an aspirating funnel placed over the flask containing the eluate. 4-(3′-Indenyl)butyronitrile-C^{14} was obtained as 0.99 g. of light yellow oil. This oil probably contained some unreacted bromide, but it was of sufficient purity for the subsequent reaction. Additional purification of nonradioactive preparations by vacuum distillation gave a yellow oil, b.p. 134–136° (0.5 mm.), 89% yield. Three crystallizations from benzene–petroleum ether (b.p. 30–60°) (3:1), followed by one crystallization from ethanol, gave colorless plates, m.p. 118–119°. The infrared spectrum showed the characteristic nitrile absorption band at 2250 $cm.^{-1}$

Anal. Calcd. for $C_{13}H_{13}N$: C, 85.2; H, 7.15; N, 7.64. Found: C, 85.0; H, 7.10; N, 7.89.

1,2,3,4-Tetrahydrofluoren-1-one-C^{14}. The nitrile (0.99 g.) was placed in a 10 ml. pear-shaped flask having a small side arm. Anhydrous ether (5 ml.) and powdered zinc chloride (0.5 g., 3.7 mmoles) were added, and a reflux condenser carrying a glass tube leading into water was attached. Dry hydrogen chloride was passed into the reaction mixture for 2 hr. by means of a tube which extended through the side arm of the reaction flask. At 0.5 hr. intervals the flow of hydrogen chloride was interrupted, and the precipitated solids were stirred manually to insure complete reaction. The ether lost by entrainment was replaced periodically. At the end of the reaction time, the solid 1,2,3,4-tetrahydrofluoren-1-imine-1-C^{14} hydrochloride was allowed to settle, and the overlying ether was drawn off. The product was washed three times by adding fresh ether, passing hydrogen chloride through the mixture and removing the ether. These washings were necessary for removal of impurities. Water (5 ml.) was then added, and air was slowly passed through the gradually warmed mixture to entrain the ether and thus prevent bumping. When the ether had been removed, the mixture was heated under reflux for 15 min. After thorough cooling, the crude product was collected on a sintered glass funnel and dried *in vacuo*. The purification of the product was accomplished by treating it with hot petroleum ether C (Skelly). When all the light-colored product had dissolved, the solution was separated from the residual brown tar.

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(15) Supplied by Volk Radiochemical Company, Chicago 40, Ill. This material had been assayed by the manufacturer to contain 3 mC. However, the final specific radioactivity of our product which was checked against a standard sample of benzoic acid-C^{14} obtained from the National Bureau of Standards indicated that the activity of the cyanide-C^{14} was actually 32% greater.

Evaporation of the solvent by a stream of air gave 0.462 g. (2.53 mmoles) of slightly yellow, crystalline 1,2,3,4-tetrahydrofluoren-1-one-1-C^{14}, m.p. 92–98°, representing a 46.5% yield for the two-step sequence. This product was sufficiently pure for the succeeding steps of the synthesis. Further crystallizations of unlabeled preparations from petroleum ether C gave white plates, m.p. 103–105°.

1-Fluorenol-1-C^{14}. 1,2,3,4-Tetrahydrofluoren-1-one-1-C^{14} (0.462 g., 2.53 mmoles) was mixed with 5 g. of sublimed fluorene and 0.241 g. of purified palladium black catalyst[16] in a 35-ml. round-bottom flask fitted with a reflux condenser. The mixture was heated under reflux by means of a Wood's metal bath for 4.5 hr. The cooled solid solution was dissolved in 40 ml. of ether and filtered through a layer of Celite into a 60-ml. centrifuge tube. The ether solution was extracted 3 times with 8-ml. portions of a 15% potassium hydroxide solution. The alkaline extract was warmed to remove any dissolved ether and was then filtered through a layer of Celite. The filtrate was acidified with concentrated hydrochloric acid and cooled. The precipitate was collected on a sintered glass funnel and dried to give 0.294 g. (1.61 mmoles) of crude 1-fluorenol-1-C^{14}, m.p. 115–119°, 64.5% yield. For the subsequent reaction further purification was not necessary. When desired, this could be accomplished by recrystallization from a large volume of hot water giving material melting at 120–121° with a resulting loss of 13% of 1-fluorenol. In large scale runs of this reaction, the materials were mixed in a ratio of 2.5 g. of palladium black catalyst, 5.0 g. of ketone and 25 g. of fluorene. With heating at the reflux temperature for 4 hr., the yield of crude 1-fluorenol was 64%. Following solution of the reaction mixture in ether, the catalyst may be recovered by filtration and reused for this reaction without purification.

2-Nitrofluorenol-1-C^{14}. 1-Fluorenol-1-C^{14} (0.294 g., 1.61 mmoles) was dissolved in 6.4 ml. of glacial acetic acid in a 25-ml. Erlenmeyer flask. The solution was stirred by a magnetic stirrer and cooled in an ice bath while a solution of 0.145 ml. (2.27 mmoles) of concentrated nitric acid in 0.145 ml. of water was added dropwise from a pipet. The pipet was washed with 1 ml. of glacial acetic acid and the wash liquid added to the reaction mixture. The flask was stoppered and the solution stirred at room temperature for 3.5 hr. The mixture was then cooled in ice. The yellow precipitate was collected on a sintered glass funnel, washed with 15 ml. of water and dried *in vacuo*. Addition of the wash water to the mother liquor caused precipitation of a second crop which was collected, washed with water, and dried. The first crop was purified by chromatography on a 1 × 18 cm. column of acid-washed, activated alumina using benzene as eluent and collecting only the leading yellow band. Crop 2 was purified in a like manner on the same column. Evaporation of the combined eluates by means of an air stream and infrared lamp gave 0.182 g. (0.80 mmole) of 2-nitro-1-fluorenol-1-C^{14}, m.p. 162–165°, 50% yield.

2-Amino-1-fluorenol-1-C^{14}. A solution of 2-nitro-1-fluorenol-1-C^{14} (0.182 g., 0.80 mmole) in 29 ml. of hot ethanol was prepared in a 50-ml. flask equipped with a reflux condenser and magnetic stirrer. Zinc dust (1.46 g.) was added and the mixture was stirred and heated under reflux while a solution of 0.4 g. of calcium chloride in 4.4 ml. of water was added dropwise. Stirring and heating were continued for 2.5 hr. at the end of which time the hot slurry was filtered through a layer of Celite into 1.6 ml. of concentrated hydrochloric acid. The zinc dust was washed with 5 ml. of ethanol. The combined filtrate and wash liquid were evaporated by means of an air stream and infrared lamp until there remained only a slurry of precipitated salts in a minimum volume of water. The salts were collected on a sintered glass funnel, washed with ether, and dried. The material was dissolved in 8 ml. of water, and the solution was filtered through a bed of Celite into 12 ml. of a 15% sodium acetate solution. The resulting suspension was cooled, and the precipitate was collected without delay. After washing with water, the product was dried *in vacuo* over calcium chloride to yield 0.0958 g. (0.49 mmole) of 2-amino-1-fluorenol-1-C^{14}, 60.5% yield.

N-(1-hydroxy-2-fluorenyl-1-C^{14})acetamide. 2-Amino-1-fluorenol-1-C^{14} (0.0958 g., 0.49 mmole) was dissolved in 22.5 ml. of hot water containing 0.09 ml. of concentrated hydrochloric acid. The solution was filtered through a coarse sintered glass funnel and cooled to room temperature. Freshly distilled acetic anhydride (0.07 ml., 0.74 mmole) was added all at once with magnetic stirring. A solution of 0.09 g. (0.11 mmole) of sodium acetate in 4.9 ml. of water was added, and the reaction mixture was stirred and cooled in an ice bath for 15 min. The gray precipitate was collected and dried. An ethyl acetate solution of the product was percolated through a 0.6 × 15 cm. column of acid-washed, activated alumina. The eluate was evaporated to dryness *in vacuo* and the residue was recrystallized by being dissolved in 3 ml. hot ethanol which was then added to 15 ml. of water. A second pass through an alumina column using the same eluent followed by recrystallization gave pure, white *N*-(1-hydroxy-2-fluorenyl-1-C^{14})acetamide, m.p. 210–212°. The yield was 0.0726 g. (0.30 mmole, 62.6%) and the specific radioactivity was 0.66 mC./mM.

Acknowledgment. We wish to thank Dr. H. T. Nagasawa for valuable suggestions and Mr. S. F. Chang for technical assistance.

RADIOISOTOPE SERVICE,
VETERANS ADMINISTRATION HOSPITAL, MINNEAPOLIS, AND THE DEPARTMENT OF PHYSIOLOGICAL CHEMISTRY,
UNIVERSITY OF MINNESOTA

(16) Obtained from the Fisher Scientific Company, Chicago, Ill.

Convenient Syntheses of 3-Indolesuccinic and 3-Indolepropionic Acids

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Received February 27, 1959

In a recent publication[1] Noland and Hammer have shown that the dibasic acid obtained by the alkaline hydrolysis of maleyldiindole[2] is 3-indolesuccinic acid. The preparation of this acid from indole and diethyl diazosuccinate has been reported previously by Jackson and Manske.[3]

The facile preparation, in 95% yield, of 3-indolealdehyde[4] prompted us to use this compound as starting material for new and convenient syntheses of 3-indolesuccinic and 3-indolepropionic acids.

Compound I, prepared by a modification of a previously described procedure,[5] when treated with potassium cyanide in refluxing ethanol[6] gave rise to 3-indolesuccinonitrile (III). The dinitrile was readily hydrolyzed with aqueous base to give an al-

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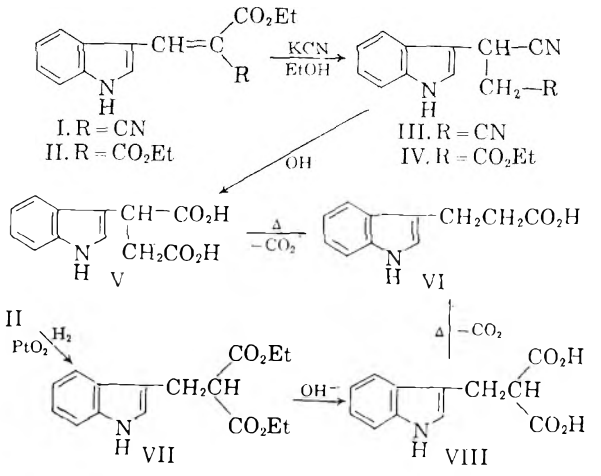

most quantitative yield of 3-indolesuccinic acid (V).

In an alternate synthesis 3-indolealdehyde was condensed with diethyl malonate in the presence of piperidine acetate,[7] and a good yield of ethyl 2-carbethoxy-3-(3-indolyl)acrylate (II) was obtained. This last compound, when treated with potassium cyanide in ethanol, yielded the cyanoester (IV), which on hydrolysis produced 3-indolesuccinic acid (V). This diacid was converted into 3-indolesuccinimide when heated with aqueous ammonia, or better with urea.

As reported by Jackson and Manske,[3] and later confirmed by Noland and Hammer,[1] 3-indolesuccinic acid is readily decarboxylated to 3-indolepropionic acid (VI) when heated above its melting point. A second convenient route to 3-indolepropionic acid was worked out according to the following sequence. Hydrogenation of compound II over platinum oxide gave diethyl 3-indolylmethylmalonate (VII),[8] which upon hydrolysis and subsquent decarboxylation led to 3-indolepropionic acid (VI).

EXPERIMENTAL[9]

Ethyl 2-cyano-3-(3-indolyl)acrylate (*I*).[5] A solution of 72.5 g. (0.5 mole) of 3-indolealdehyde,[4] 56.5 g. (0.5 mole) of ethyl cyanoacetate and 5 ml. of piperidine in 875 ml. of ethanol was heated at reflux for 10 min. and cooled, yielding 102.5 g. of bright yellow crystalline product melting at 164–165°. Evaporation of the filtrate yielded a second crop of 15 g., m.p. 162–164°; total yield 117.5 g. (98%); reported m.p. 165°.[5]

Ethyl 2-carbethoxy-3-(3-indolyl)acrylate (*II*). To a solution of 48 g. (0.3 mole) of diethyl malonate in 600 ml. of benzene there was added 43.5 g. (0.3 mole) of 3-indolealdehyde,[4] 6 ml. of piperidine, and 9 ml. of glacial acetic acid. The mixture was heated at reflux for 4 hr. while the theoretical amount (5.4 ml.) of water was collected in a Dean-Stark trap. After removal of the benzene under reduced pressure the residue was recrystallized from ethanol-water to yield 60 g. (70%) of pale yellow crystalline product having m.p. 99–100° (with shrinking at 92°).

Anal. Calcd. for $C_{16}H_{17}NO_4$: C, 66.88; H, 5.96. Found: C, 67.04; H, 5.87. Infrared (KBr) (μ): 3.08 (NH); 5.82, 5.92 (ester).

3-Indolesuccinonitrile (III). A mixture of 96 g. (0.4 mole) of ethyl 2-cyano-3-(3-indolyl)-acrylate and 52 g. (0.8 mole) of potassium cyanide in 500 ml. of 90% ethyl alcohol was stirred and heated at reflux for 3 hr. After being cooled in ice the mixture was filtered and the solid washed with 80 ml. of 95% ethanol. The filtrate and washings were combined and concentrated under reduced pressure to one half of the original volume; the concentrated solution was heated to 65–70°, diluted with an equal volume of water, heated again to 65–70° and allowed to cool slowly overnight at 5–10°. The dark brown crystalline product was collected and dried; yield 59 g. of colored crystals melting at 113–116°. The crystalline solid was triturated with a small amount of cold ether, filtered, and recrystallized from 50% aqueous methanol, yielding 52 g. (66%) of colorless crystals melting at 117–118°.

Anal. Calcd. for $C_{12}H_9N_3$: C, 73.83; H, 4.65; N, 21.5. Found: C, 73.80; H, 4.65; N, 21.2. Infrared (KBr) (μ): 3.00 (NH); 4.45 (CN).

The picrate of 3-indolesuccinonitrile was prepared by adding a boiling solution of picric acid in ethanol to a boiling solution of the dinitrile in ethanol. The cooled solution was diluted with water until crystallization began. The yellow crystals were collected by filtration and recrystallized from ethanol; the pure yellow crystals melted at 117–118°.

Anal. Calcd. for: $C_{18}H_{12}N_6O_7$: C, 50.95; H, 2.85. Found: C, 51.50; H, 3.02.

Ethyl 3-cyano-3-(3-indolyl)propionate (IV). To a solution of 69 g. (0.24 mole) of ethyl 2-carbethoxy-3-(3-indolyl)-acrylate (II) in 300 ml. of 90% ethanol there was added 31 g. (0.48 mole) of potassium cyanide and the mixture was stirred at reflux for 2 hr. It was cooled, filtered, and the solid was washed with 25 ml. of 95% ethanol. The filtrate and washings were combined, diluted with 800 ml. of water and the resultant crystalline precipitate was collected and dried; yield 25.5 g. (61%) of IV having m.p. 108–110°. After successive recrystallizations from ethyl acetate and benzene the analytical sample had m.p. 110–111°.

Anal. Calcd. for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.82. Found: C, 69.82; H, 5.76. Infrared (KBr) (μ): 2.90 (NH); 4.45 (CN); 5.82 (ester).

3-Indolesuccinic acid (V). A suspension of 39 g. (0.2 mole) of III, or 48.4 g. (0.2 mole) of IV, in 330 ml. of 15% aqueous potassium hydroxide solution was heated at reflux for 3 hr. At the end of this period a clear solution was obtained and only a small amount of ammonia was being evolved. The resultant dark solution was treated with charcoal while still hot, filtered, cooled, and acidified to *p*H 2 with concentrated hydrochloric acid. The white crystalline product was collected, washed with cold water, and dried; yield 44.5 (95%), m.p. 197–200° (dec., with gas evolution). An analytical sample, recrystallized from water, melted at 204–205° (dec., gas evolution); reported m.p. 199°[3] and 195–197°.[1]

Anal. Calcd. for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.72; neut. equiv., 116.6. Found: C, 62.10; H, 4.88; neut. equiv. 116.7. Infrared (KBr) (μ): 2.92 (NH); 5.98 (C=O).

Diethyl 3-indolesuccinate was prepared in 93% yield from V, ethanol, and dry hydrogen chloride and had m.p. 80–81°, a value in agreement with those previously reported.[1,3]

This diester was also prepared by saturating a chilled

(7) Whereas ethyl cyanoacetate condensed readily with 3-indolealdehyde in the presence of piperidine, the same catalyst failed to bring about the condensation with diethyl malonate.

(8) (a) H. R. Snyder, C. W. Smith, and J. M. Stewart, *J. Am. Chem. Soc.*, 66, 200 (1944). (*b*) D. I. Weisblat and D. A. Lyttle, *J. Am. Chem. Soc.*, **71**, 3079 (1949). (c) G. Stork and G. Singh, *J. Am. Chem. Soc.*, **73**, 4742 (1951).

(9) All melting points are uncorrected. Analyses by R. M. Downing, infrared by D. Evans.

solution of III or IV in ethanol with dry hydrogen chloride, diluting with water to the point of turbidity and storing for 24 hr. at 5–10°. This procedure yielded 88 to 90% of the desired material; m.p. 79–81°.

Dimethyl 3-indolesuccinate[2] was prepared either from the diacid or the dinitrile by treating them with dry hydrogen chloride in methanol. The dimethyl ester was obtained in yields of 85–95% and melted at 73–76° after recrystallization from a benzene-*n*-pentane mixture; reported m.p. 74°.[2]

Anal. Calcd. for $C_{14}H_{15}NO_4$: C, 64.36; H, 5.79. Found: C, 64.65; H, 6.06.

3-Indolesuccinimide. The following modification of the method used by Shaw[10] for the preparation of 3-indoleacetamides was employed. An intimate mixture of 35 g. (0.15 mole) of 3-indolesuccinic acid (V) and 70 g. (0.46 mole) of urea in a flask fitted with an air condenser was introduced into an oil bath at 160°. The bath temperature was raised to 185° during 30 min. and maintained at 180–190° for 2.5 hr. Brisk evolution of ammonia was evident during the first part of the final heating period. The hot melt was diluted to 250 ml. with water, cooled and filtered. The crude product was recrystallized from methanol with charcoaling, yielding 17 g. (53%) of white crystals of m.p. 197–198°. A mixed m.p. between this product and V gave considerable depression.

Anal. Calcd. for $C_{12}H_{10}N_2O_2$: C, 67.29; H, 4.67; N, 13.1. Found: C, 67.33; H, 4.70; N, 12.8. Infrared (KBr) (μ): 2.92 (indole NH); 5.50, 5.65, 5.86, and 5.95 (C=O).

A small amount of 3-indolesuccinimide was also obtained by gradually heating a sample of 3-indolesuccinic acid (V) to 240° in concentrated ammonium hydroxide; it had m.p. 194–195°. The m.p. of a mixture of this material with that prepared from V and urea was not depressed.

Diethyl 3-indolylmethyl malonate (VII). Hydrogenation of a sample of II in ethanol over platinum oxide at 50 p.s.i. gave a 62% yield of diethyl 3-indolylmethylmalonate (VII)[8], m.p. 61–63° (recrystallized from benzene-*n*-pentane). An analytical sample was recrystallized from ethanol-water and had m.p. 63–65°; reported 62°.[8a,b]

Anal. Calcd. for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62. Found: C, 66.68; H, 6.76. Infrared (KBr) (μ): 2.97 (NH); 5.77 and 5.83 (C=O).

3-Indolylmethylmalonic acid (VIII). A 2.8-g. (0.01 mole) sample of diethyl 3-indolylmethylmalonate (VII) was heated under reflux for 1 hr. in 25 ml. of 15% potassium hydroxide solution. The solution was charcoaled, filtered, cooled, and acidified to *p*H 2 with concentrated hydrochloric acid to yield 1.6 g. (89%) of reddish 3-indolylmethylmalonic acid (VIII);[8] m.p. 182–184° (dec., with evolution of gas). An analytical sample, recrystallized from water, was still reddish; m.p. 185–187° (dec., gas evolution); reported 178° (dec.).[8a]

Anal. Calcd. for $C_{12}H_{11}NO_4$: C, 61.80; H, 4.74. Found: C, 62.08; H, 4.94.

3-Indolepropionic acid (VI). Pyrolysis of a sample of 3-indolesuccinic acid (V) for 2–3 minutes at 205° gave a vigorous evolution of carbon dioxide; the residue was cooled and recrystallized from 20% ethanol (charcoal). The colorless crystals thus obtained melted at 133–134° either alone or upon admixture with an authentic sample of 3-indolepropionic acid.

3-Indolylmethylmalonic acid (VIII) was pyrolyzed at 190–200° to yield VI in a yield of 46%, m.p. 132–134° either alone or upon admixture with authentic VI.

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(10) E. Shaw, *J. Am. Chem. Soc.*, **77**, 4319 (1955).

Metalation of Polystyrene[1]

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Received March 2, 1959

This metalation of polystyrene was done in the hope of developing a method for introducing metal atoms on the alpha (to phenyl) carbon atoms of the chain. The reaction proved easier than expected. Under some conditions or in some fractions, 86 to 94% of the maximum possible amount of metalation on a chain was realized. The project was terminated before the fine conditions for control could be worked out, but the results deserve mention because they represent a new chemical attack at specific points on this polymer. The reaction also provides a new base for graft polymerization or chemical processes on polystyrene.

The reagent was potassium metal and sodium oxide[2] although the very recent experience[3] with amyl- and phenyl-potassium suggests that those reagents might be equally good or even better because they are finely divided and leave no inorganic residue other than potassium chloride or an alkoxide. Benzene was the medium, that solvent having been found satisfactory in a series of preliminary experiments with cumene, a low molecular weight pattern molecule. After a stipulated time the mixture was carbonated. Then the solid was digested with hot water to remove the carboxylate. Mineral acid precipitated the carboxylated polymer. The dried polymer was weighed, titrated with alkali to determine the neutralization equivalent, and mixed with potassium bromide for infrared measurements.

Metalation was about as easy as with cumene itself. Time was very important. At the end of three hours, under approximately comparable conditions, the weights of carboxylic acid were 0.7 and 0.5 gram for cumene and the polymer, respectively. The neutralization equivalent of the polymer carboxylate indicated that 94% of the available positions on the metalated chain had been occupied. In a longer time (15 hr.) the polymer took up 42% of the potassium, and 36% of the polymer was recovered as carboxylate (14.4 g.) for which 89% of the maximum possible metalation had taken place.

The potassium ion should be on the carbon alpha to the phenyl group because metalation of alkylaryl hydrocarbons by this reagent has occurred[2] only at that place. The absorption at 1700 cm.$^{-1}$ in the infrared (Fig. 1) accorded with this view. The position of absorption was similar to that found for other acids of that type. The intensity of absorption was very high, being much greater at

(1) This work was performed as part of a research project sponsored by the National Science Foundation.

(2) C. E. Claff, Jr., and A. A. Morton, *J. Org. Chem.*, **20**, 444, 981 (1955).

(3) A. A. Morton and E. J. Lanpher, *J. Org. Chem.*, **23**, 1639 (1958).

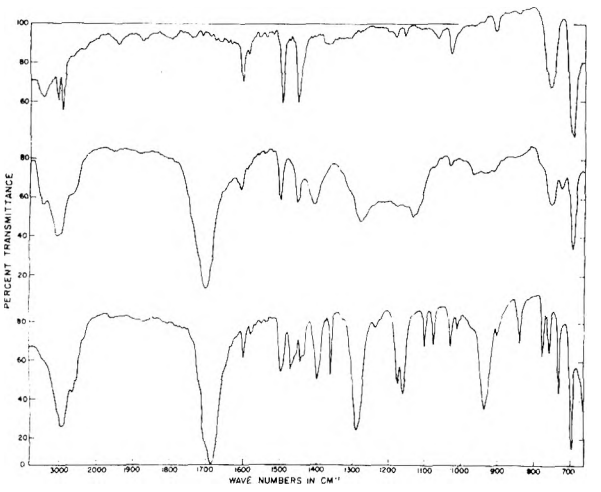

Fig. 1. Comparison of the infrared absorption of polystyrene, carboxylated polystyrene, and α-phenylisobutyric acid as shown by the top, middle, and bottom lines, respectively. The intensity of the absorption of the carbonyl of the carboxyl group at 1700 cm.$^{-1}$ should be compared with that for monosubstitution on the benzene ring at 700 cm.$^{-1}$ The strong bands at 1290 cm.$^{-1}$ for a carboxyl group and at 935 cm.$^{-1}$ for OH deformation in the low molecular weight carboxylic acid (lowest line) are greatly reduced in intensity in the polymer carboxylic acid

that wave length than at any other place in the spectrum.

EXPERIMENTS

The reagent and general conditions. In all experiments 8.5 g. of potassium with 56 g. of sodium oxide was used. Benzene (usually 250–300 ml.) was the medium. The apparatus was a 1-l. creased flask with high speed (5000 r.p.m.) stirring as is the common practice[2,3] in this laboratory for heterogeneous reactions.

Metalation of cumene. Cumene (40 g.), which previously had been treated with amylsodium to remove impurities, was metalated in 300 ml. of benzene for 3 hr. at 75–80°. The color of the mixture changed progressively from grey to pinkish brown to dark tan to blackish brown. After being carbonated, the mixture was allowed to stand overnight before addition of water. The hydrocarbon layer was separated and the aqueous portion was extracted twice with ether before being acidified. The carboxylic acids were recovered by extraction with ether. The yield was 0.7 g. or 2% calculated on the metal. The crude acid melted at 72–78° and had a neutralization equivalent of 165.1 (theory 164). Recrystallization from water raised the melting point to 80–81°, identical with the value obtained from previous metalations in heptane.[2,4]

A similar experiment with 95 g. of cumene in 250 ml. of benzene yielded 1.0 g., or 3.4%. In 15 hr. with 200 g. of cumene the yield was 6.3 g. or 24%. Metalation of cumene in benzene was less than it was in cumene itself as might be expected; under conditions similar to the 3-hr. experiment the yield was 3 g. or 11%, and similar to the 15-hr. run it was 14 g. or 40%. The melting points of all of these products were similar to that described for the first experiment in this section.

Metalation of polystyrene. Polystyrene (40 g.) in 500 ml. of benzene was metalated for 3 hr. at 75–80°. The color changed from light brown to tan to chocolate brown. The carbonated product was treated with water as in the case of the metalated cumene, but the benzene was removed by warming on a steam bath. Then the solid was digested for a day with a liter of water to which a few pellets of sodium hydroxide had been added. The aqueous extract was acidified and the recovered polymer was washed and dried. The yield was 0.5 g. and the neutralization equivalent was 234, a value which showed that the metalation of this water-soluble fraction had been 59% complete.

This experiment was repeated with 95 g. of polymer. The yield was 0.2 g. and the neutralization equivalent was 161.5 which corresponded to 94% complete metalation of that fraction.

Several metalations were carried out for 15 hr. With 29 g. of polystyrene in 300 ml. of benzene the yield after three extractions of the carboxylated polymer was 14.4 g. which had a neutralization equivalent of 172 corresponding to 89% complete metalation of that fraction. With 62.5 g. of polystyrene the yield was 17.1 g. of carboxylated polymer which had a neutralization equivalent of 178, corresponding to 86% metalation of the available positions in that fraction. With 200 g. of polymer the yield was 3 g. and the neutralization equivalent was 220, corresponding to 65% complete metalation in a chain.

The reduction in yield as larger quantities of polystyrene were used may be an illusion caused by distribution of the metalating action to other chains and failure to extract polymer which contained only a few carboxyl groups per chain. No claim is made that the extraction removed all of the carboxylated polymer. However, in one instance where the yield was very low, the residue was given an additional extraction with alcoholic sodium hydroxide without removal of any more carboxylated polymer.

Infrared measurements. The polymer was ground with potassium bromide in proportion to make a 1% pellet. The spectrum is shown in Fig. 1 together with one of polystyrene (top) and of α-phenylisobutyric acid (bottom) made under the same conditions and at the same concentration. The absorption at 1700 cm.$^{-1}$ is characteristic[5] for the carbonyl of the carboxyl group and its intensity confirms the finding of a large amount of metalation on each chain. Its position accords with other evidence that the carboxyl is on a carbon atom adjacent to the phenyl group, the absorption for that position being a little different from that shown by a carboxyl on the ring. Table I shows a comparison of the polymer carboxylic acid with other acids which have a somewhat similar structure and have been observed[4] in this laboratory.

TABLE I

INFRARED COMPARISON OF ABSORPTIONS BY THE CARBONYL OF THE CARBOXYL GROUP IN VARIOUS CARBOXYLIC ACIDS OF SOMEWHAT SIMILAR STRUCTURES

Hydrocarbon Metalated	Aliphatic Carboxyl, cm.$^{-1}$	Carbon Component of Acid	Aromatic Carboxyl, cm.$^{-1}$
Cumene	1691	—$(CH_3)_2CC_6H_5$	
Cumene		$(CH_3)_2CHC_6H_4$—	1681
n-Butylbenzene	1705	—$(C_3H_7)CHC_6H_4$—	1685
p-Cymene	1712	—$CH_2C_6H_3CH(CH_3)_2$	
Polystyrene	1700	—$(RCH_2)_2CC_6H_5$[a]	

[a] R symbolizes a section of the polystyrene chain.

Acknowledgments. The authors are greatly indebted to James Howard for carrying out all of the metalations described in this note, to Marianne

(4) A. A. Morton and J. L. Eisenmann, *J. Org. Chem.*, **23**, 1469 (1958).

(5) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley and Sons, Inc., New York, N. Y., 1954.

Taylor for the infrared measurements, to the Dow Chemical Company for the polystyrene used in most of the experiments, and to the E. I. du Pont de Nemours & Co., Inc. for the sodium oxide.

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Preparation of D-Propylene Glycol and Oxide

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Received March 2, 1959

By the reduction of acetol benzoate, readily prepared from chloroacetone and sodium benzoate, with fermenting yeast solution, optically pure D-propylene glycol 1-benzoate was obtained in 65% yield. Saponification produced D-propylene glycol in 60% yield. This contrasts to yeast reduction of acetol itself, which yields L-propylene glycol.[1]

Treatment of the D-glycol with anhydrous hydrogen bromide gave the bromohydrin, $[\alpha]_D^{24}$ +9.90° (in $CHCl_3$), which was converted by alkali to D-propylene oxide, $[\alpha]_D^{21}$ −6.21° (2% in $CHCl_3$).

EXPERIMENTAL

D-Propylene glycol 1-benzoate. Into a 3-l. two-necked round-bottomed flask, provided with a gas trap and a mechanical stirrer, a solution of 100 g. of sucrose in 450 ml. of tap water was placed. To this solution, a paste of 40.6 g. of Fleischmann's dry yeast in 140 ml. of tap water was added. The mixture was allowed to stand at room temperature until a lively evolution of gas started. To this vigorous fermenting solution, 4.5 g. of acetol benzoate[2] was added and the mixture was allowed to stand at room temperature until the reaction subsided. The flask was then transferred to an incubator at 32° (or at room temperature for a longer time). The reaction was generally completed when all of the yeast had settled. Most of the clear solution was separated from the yeast by a siphon. The last portion of the solution was filtered. The combined solution was extracted with ether (3 × 150 ml., tech. grade) and the ethereal solution was washed with 3% aqueous sodium carbonate solution, water, and dried. After the removal of the solvent, the yellowish oil was distilled under reduced pressure, b.p. 139–140° (5 mm.). The distillate solidified after cooling. It was recrystallized from ether (Mallinckrodt, anhyd.) as white needles by dissolving the crude product in ether at room temperature and cooling the ethereal solution with an acetone–Dry Ice bath, m.p. 42–42.5°; yield, 64–66%, $[\alpha]_D^{24.2}$ + 21.8° (in $CHCl_3$).

The compound obtained did not give a good analysis, even after it had been purified alternatively by vacuum distillation and recrystallization (each twice).

(1) The reduction of the benzoate in the opposite sense to the glycol was predicted by Dr. V. Prelog (private communication).

(2) For the preparation of acetol benzoate, Adams and Govindacharis' procedure was followed [*J. Am. Chem. Soc.*, **72**, 158 (1950)] with the following modification. The combined ethereal solution was washed with ice-cold 3% sodium carbonate solution, water, and dried. It is very important that no trace of benzoic acid remain in the acetol benzoate. Otherwise the yeast will be killed during the fermentation.

Anal.: Calcd. for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 67.17, 67.32, 67.39; H, 6.87, 6.84, 6.77.

D-Propylene glycol. Optically-active propylene glycol 1-benzoate (40 g.) was added gradually with constant shaking to 20 g. of 50% alkali solution. An additional 10–15 ml. of water was added and the cakelike sodium benzoate was mashed with a spatula. The reaction mixture was refluxed in an oil bath at 125° for 3 hr. After cooling, 100 ml. of ether was poured in and the mixture was filtered. The precipitate was washed with 10 ml. of absolute ethanol. The filtrate was extracted with ether for 9 hr. The ethereal layer obtained was dried over anhydrous magnesium sulfate and evaporated to yield 10.1 g. (60%) of propylene glycol, b.p. 92° (14 mm.), $n_D^{25.7}$ 1.4334, $[\alpha]_D^{24.2}$ + 30.0° (in $CHCl_3$). (For *l*-propylene glycol, b.p. 86–88° (9–10 mm.), $[\alpha]_D^{24.4}$ −28.6° (in $CHCl_3$); −14.9° (pure state, dm.), d^{24} 1.030, n_D^{24} 1.4355.)

D-Propylene oxide. Levene's synthesis[3] for L-propylene oxide was used. D-Propylene bromohydrin was prepared by passing dry hydrogen bromide through D-propylene glycol at 0°; yield, 60%, b.p. 57–58° (19 mm.), n_D^{25} 1.4765 $[\alpha]_D^{24}$ +9.90° (in $CHCl_3$). (For L-propylene bromohydrin, n_D^{25} 1.4775, $[\alpha]_D^{24}$ −10.53° (in $CHCl_3$) or −3.37° (pure bromohydrin), $d^{24.5}$ 1.541.)

The D-propylene bromohydrin was then cyclized to D-propylene oxide with 45% (by weight) aqueous potassium hydroxide, b.p. 35°, $[\alpha]_D^{21}$ −6.21° (2% in $CHCl_3$). [*l*-Propylene oxide, $[\alpha]_D^{21}$ +7.05° (2% in $CHCl_3$); +14.5° (38% in ether)].

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(3) P. A. Levene and A. Walti, *J. Biol. Chem.*, **68**, 415 (1926).

Relative Reactivities of Toluene and Toluene-α,α,α-d_3 in Hydrogen-Deuterium Exchange

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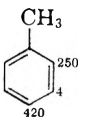
March 2, 1959

Recent exchange studies[2] carried out in this laboratory have led to the following values for the partial rate factors for hydrogen-deuterium exchange in the case of toluene:



These exchange studies were conducted at 70° in a trifluoroacetic acid medium. Under these conditions, exchange occurs only in the aromatic nucleus. This fact was demonstrated by oxidizing a sample of randomly deuterated toluene to benzoic acid with aqueous alkaline permanganate. There was no loss of deuterium in this transformation. Infrared absorption studies, though less sensitive, also indicated the absence of side-chain deuterium in the randomly deuterated toluene samples. These

(1) Abstract of part of Ph.D. thesis submitted to the University of Minnesota, June 1958.

(2) W. M. Lauer, G. Matson, and G. Stedman, *J. Am. Chem. Soc.*, **80**, 6433, 6437, 6439 (1958).

circumstances made it feasible to include the study of the deuteration of toluene-α,α,α-d_3, since determination of the deuterium content of the benzoic acid produced on oxidation provides a comparison of the relative rates of nuclear deuteration of toluene and toluene-α,α,α-d_3.

Several interesting studies dealing with secondary isotope effects have been reported.[3] These studies have shown that a measurable secondary isotope rate effect is transmitted across the aromatic nucleus. Thus, for example, p-$CD_3C_6H_4CH(Cl)C_6H_5$ and p-$CH_3C_6H_4CH(Cl)C_6H_5$ manifest slightly different solvolysis rates; the introduction of deuterium into the p-methyl group definitely slows the rate of solvolysis. However, only the work of Swain and his co-workers dealt directly with the secondary isotope effect in nuclear substitution. These investigators found that the secondary isotope effects on the rates of nuclear nitration, mercuration and bromination due to isotopic substitution for hydrogen in the methyl group of toluene are 3% per deuterium atom or less. Our results showed that the substitution (90%) of deuterium for the three hydrogens in the methyl group of toluene decreased the nuclear deuterium-hydrogen exchange rate approximately 5% or about 2% per deuterium atom. The size of this effect is dependent upon the detailed mechanism of the process and since it is intermediate between the values found by Swain, Knee, and Kresge for nitration and bromination in 85% acetic acid, it may perhaps be concluded that deuteration in trifluoroacetic acid follows an intermediate course. On the other hand, these differences in the secondary isotope effect between various electrophilic aromatic substitution reactions are quite small and may be without mechanistic significance.

EXPERIMENTAL

Toluene-α,α,α-d_3 (2.7 D) was prepared according to the procedure of Renaud and Leitch.[4] Acetic anhydride (3.0 moles) was heated with magnesium turnings (10 g.) under reflux for 24 hr. The anhydride was then decanted and treated with powdered zinc (10 g.), carbon tetrachloride (10 ml.), and phosphorus pentoxide (0.1 g.). Deuterium oxide (99.5%, 3.2 moles) was added slowly during a period of 1.5 hr. The mixture was then stirred mechanically for 3 hr. at 60°. Fractional distillation yielded acetic acid-d (b.p. 116–118°, n_D^{25} 1.3706, 250 g.). A mixture of anhydrous ether (600 ml.), acetic acid-d (170 g., 2.78 moles), and zinc dust (110 g.), cooled to 3°, was then treated with freshly distilled benzotrichloride (90 g.) dissolved in dry ether (300 ml.). The time of addition was 3 hr. and after the addition was complete stirring was continued for 3 hr. A white precipitate formed in the reaction flask. Water (500 ml.) was added and the reaction mixture was filtered. The ether layer was washed with water (300 ml., 3×), aqueous sodium bicarbonate (10%; 250 ml., 2×), and finally with water (300 ml.). The ether solution on distillation yielded toluene-α,α,α-d_3 (b.p. 109–110°, n_D^{25} 1.4929, 29%). A deuterium assay indicated 2.70 atoms of deuterium per molecule. An alkaline permanganate oxidation gave benzoic acid containing only the normal level of deuterium per molecule.

The infrared Spectrum (Perkin-Elmer model 21) showed no absorption for ring deuterium in the 2245–2285 cm.$^{-1}$ region. In addition, there is no absorption at 617, 640, and 830 cm.$^{-1}$ which are characteristic of ortho, meta, and para deuterotoluenes, respectively.

Determination of deuterium. The toluene samples were oxidized with alkaline permanganate and the benzoic acid obtained was burned in a stream of oxygen. The water produced was passed over hot zinc and the gas was analyzed using a mass spectrometer.[5] It had been shown earlier that toluene deuterated in the ring is oxidized in the presence of alkali to benzoic acid without the loss of any deuterium.

Calculations. At the temperature of the reduction (zinc), the equilibrium constant for the following reaction is approximately 4.

$$H_2 + D_2 \rightleftarrows 2HD$$
$$(a - x)\ (b - x)\ 2x$$

At equilibrium

$$\frac{(2x)^2}{(a - x)(b - x)} = 4 \text{ and } x = \frac{ab}{a + b}$$

The HD/H_2 ratio, $R = 2x/(a - x)$ and $x = aR/(R + 2)$; consequently $b = aR/2$. The mole fraction of deuterium X_D in the deuterated compound may be expressed by the following equation:

$$X_D = \frac{D}{D + H} = \frac{2x + 2(b - x)}{2x + 2(b - x) + 2x + 2(a - x)} = \frac{b}{a + b} = \frac{R}{R + 2}$$

Since the mole fraction of deuterium of an unchanged sample is 0.00015, the mole fraction of deuterium introduced becomes $R/(R + 2) - 0.00015$. It is often convenient to express the amount of deuterium introduced as the mole fraction of monodeuterated compound formed, ArD/(ArD + ArH). Thus, in the case of monodeuterobenzoic acid, C_6H_4DCOOH, the mole fraction of deuterium is $^1/_6$. An HD/H_2 value of 0.01522 yields a value $6/1[R/R + 2 - 0.00015]$ or 0.045; *i.e.*, $C_6H_{4.955}D_{0.045}COOH$.

Deuteration studies. The deuterating reagent was prepared as follows: Deuterium oxide (99.7%, 5 g., 0.2497 mole) was diluted to 100 ml. with trifluoroacetic acid (Eastman Kodak Co., White Label).

Toluene (1.38 g., 0.0150 mole) or toluene-α,α,α-d_3 (2.7 D) (1.43 g., 0.0150 mole) was dissolved in the deuterating agent (3.00 ml.). Solutions were prepared in glass ampoules (10 ml.), which were sealed immediately and placed in a bath maintained at a temperature of 70.0 ± 0.1°. Deuterations were carried out for 25, 50, 72, and 98 hr. At the end of these periods, the ampoules were opened and the contents poured into ice and water. The hydrocarbon layer was then separated and washed twice with aqueous potassium hydroxide solution (10%, 5 ml.).

The hydrocarbon samples were then oxidized by means of an aqueous alkaline permanganate solution. Dr. Gale Matson of this laboratory found that there was no loss of deuterium

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(5) We are indebted to Prof. A. O. C. Nier and his colleagues of the department of physics for the determination of the HD/H_2 ratios.

in this process. This statement is based on the finding that a sample of randomly deuterated toluene HD/H_2 ratio of 0.00862; $C_6H_{4.967}D_{0.033}CH_3$ gave benzoic acid HD/H_2 ratio of 0.0114; $C_6H_{4.967}D_{0.033}COOH$ on oxidation under these conditions.

An analysis of the samples of benzoic acid obtained in the present study follows:

Time, Hr.	Toluene		Toluene-α,α,α-d_3 (2.7 D)	
	HD/H_2	$C_6H_{(5-n)}D_nCOOH$, n	HD/H_2	$C_6H_{(5-n)}D_nCOOH$, n
25	0.01522	.044	0.01424	.042
50	0.02837	.083	0.02684	.078
72	0.03899	.113	0.03747	.109
98	0.05078	.148	0.04843	.141

Acknowledgment. This work was supported by the Atomic Energy Commission, Contract AT(11-1) 478.

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Solubility Classification Test for the Differentiation of Strong and Weak, Water-insoluble Organic Bases

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Received March 4, 1959

Solubility classification tests for the differentiation of strong and weak, water-insoluble acids have long been a part of the customary procedure for identification of organic compounds; however, similar tests for the differentiation of strong and weak, water-insoluble organic bases are not described in the most recent editions of several widely adopted texts for qualitative organic analysis.[1-3] The absence of such tests probably is due to the lack of a simple suitable reaction solvent which would be capable of differentiating bases in a manner analogous to the differentiation of acids by sodium bicarbonate solution.

A reaction solvent that has been found suitable for such a differentiation of bases is a sodium acetate–acetic acid solution buffered at a *p*H of 5.5. Aliphatic amines (K_b 10^{-3} to 10^{-5}) are soluble in this solution, but aromatic amines and other weak bases (K_b about 10^{-10}) are not. Thus, by a simple extension of the solubility classification tests now commonly used, basic compounds may be separated into two classes by reference to their solubilities in this reagent, class B_1 to include those that are soluble and class B_2 those that are insoluble. A series of water-insoluble bases whose classifications have been determined on this basis are listed in Table I.

TABLE I
SOLUBILITIES* OF WATER-INSOLUBLE BASES IN 5% HCl AND NaOAc-HOAc BUFFER[b]

Base	5% HCl	NaOAc–HOAc	Class
Tri-*n*-butylamine	+	+	B_1
N,*N*-dibenzylamine[c]	+	+	B_1
N-methyl-3-piperidylphenylcarbinol[d,e]	+	+	B_1
N-benzyl-4-piperidylphenylcarbinol[d]	+	+	B_1
N-methyl-3-benzyl-1,2,5,6-tetrahydropyridine[d]	+	+	B_1
Aniline	+	−	B_2
N,*N*-dimethylaniline	+	−	B_2
p-toluidine	+	−	B_2
p-anisidine	+	−	B_2
4-benzoylpyridine	+	−	B_2

* 0.2 ml. of liquids and 0.1 g. of solids in 3 ml. of solvent. [b] 2.0*M*. in NaOAc and 0.4*M*. in HOAc. [c] Insoluble salts precipitated from the reaction solvents. [d] Obtained through the courtesy of Glenn H. Warner, Teaching Fellow, Univ. of New Hampshire. [e] Although most of this material dissolved in NaOAc–HOAc buffer, a small quantity remained undissolved.

This same reaction solvent is also useful for the separation of a mixture of aromatic and aliphatic amines. In connection with a separate study where such mixtures are usually encountered,[4] a procedure utilizing sodium acetate–acetic acid buffer for the separation of α-*p*-methoxyphenylethylamine from *N*-ethyl-*p*-methoxyaniline was found to be more satisfactory than one previously employed.[5,6]

EXPERIMENTAL

Preparation of sodium acetate–acetic acid buffer. A solution of the desired *p*H (5.5) was prepared by dissolving 164 g. (2 moles) of anhydrous sodium acetate and 24 g. (0.4 mole) of acetic acid in sufficient water to make 1 liter of solution.

Solubility classification tests. The limits of solubility used were those described by Shriner, Fuson, and Curtin.[7] The tests were performed by placing 0.2 ml. of the amine (0.1 g. of solids) in 3 ml. of the appropriate reaction solvent, followed by vigorous shaking of the mixture. If the amine dissolved completely or was found to be appreciably more soluble than in water alone it was recorded as soluble.

Separation of mixtures of aliphatic and aromatic amines. A 50-ml. sample of a solution of α-*p*-tolylethylamine and *N*-ethyl-*p*-toluidine in ether, on titration by potentiometric techniques, was found to contain 0.78 m.equiv. of the former

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(2) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *The Systematic Identification of Organic Compounds*, 4th ed., John Wiley and Sons, Inc., New York, 1956.

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(7) Ref. 2, pp. 65–7.

and 0.62 m.equiv. of the latter. A second 50-ml. sample of the same solution, after extraction with three 20-ml. portions of sodium acetate–acetic acid buffer and drying with Drierite, was found to contain only *N*-ethyl-*p*-toluidine (0.57 m.equiv.) on titration by the same techniques.

A complete physical separation of a mixture of 1.40 g. (9.0 m.equiv.) of α-*p*-methoxyphenylethylamine and 1.03 g. (6.8 m.equiv.) of *N*-ethyl-*p*-methoxyaniline, dissolved in 225 ml. of ether, was accomplished by this method. The ether solution containing the amines was extracted with three 80-ml. portions of sodium acetate–acetic acid buffer. After drying the ether layer over anhydrous sodium carbonate, the ether was removed, and the residue was distilled to yield 0.46 g. of *N*-ethyl-*p*-methoxyaniline, b.p. 122–123° (8 mm.), $n_D^{25.5}$ 1.5503 (reported,[5] n_D^{26} 1.5494), hydrochloride m.p. 150–152°, (reported[5] 150–152°).

The sodium acetate–acetic acid extracts were combined and basified with 20 ml. of 20% sodium hydroxide solution. The resulting mixture was extracted with three 80-ml. portions of ether, and the ether extracts were combined and dried over Drierite. After removal of the ether, the residue was distilled to yield 0.98 g. of α-*p*-methoxyphenylethylamine, b.p. 117–118° (10 mm.), n_D^{27} 1.5282 (reported, n_D^{26} 1.5238,[5] n_D^{25} 1.5280[8]), hydrochloride m.p. 158.5–160° (reported,[5] 158–160°).

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Simple Method for Removal of Peroxides from Diethyl Ether[1]

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Received March 20, 1959

The formation of peroxides in stored ether constitutes an explosive hazard and a recurring introduction of impurity. To avoid peroxide formation, water and reducing agents are usually incorporated into commercial ether of all but the highest quality. In the latter cases, where the presence of reducing agent, *e.g.*, 2–4% ethanol, might be objectionable, it is expected that the ether will be freshly distilled before use; the higher boiling fraction will contain the peroxides. Because of the explosive hazard involved in too greatly concentrating peroxides, it is always necessary to leave a fairly large quantity of ether in the residue to be discarded.

A method has been found by which the peroxides may be quickly and simply removed from high quality ether samples, with no need for distillation apparatus and with only negligible loss of ether. The method presumably depends upon the slight ionization of the peroxides into hydrogen ion and the peroxidic anion. The latter, it has been found, is readily and firmly bound to the strong anion exchanging resin, Dowex 1, the Dowex being prepared in the hydroxyl form. The method has the additional advantage that, if desired, the peroxides may be eluted off into aqueous solutions.

EXPERIMENTAL

Four g. of Dowex 1 (hydroxyl form) were formed into a column in a 10 mm. (I.D.) tube, the constricted bottom being plugged with glass wool and the top overlaid with a circle of Schleicher and Schuell No. 410 filter paper. Approximately 20 ml. of ether were poured on the column. The ether was a sample of "Baker Analyzed" reagent grade anhydrous ether, with water content of 0.04% and ethanol of 0.01%, according to the label. The 5-lb. bottle had first been opened approximately 3 months previously. Although the ether was not then specifically tested for peroxides, it contained, again according to the label, <0.001% peroxide (as H_2O_2).

As the ether flowed through the column, the effluent was discarded until a simple drop evaporation test indicated that a negligible amount of water was left. The ether effluent was then collected. Both the effluent ether and the original ether were tested for peroxides by the KI test described in American Chemical Society specifications.[2] In this test, 10 ml. of ether are shaken with 1 ml. of fresh 10% KI solution. After 1 min., a yellow color indicates the presence of peroxide. Upon performing this test upon the effluent ether, no color was detectable in either the ether or the aqueous phase. A sample of the original ether, however, showed a strong yellow color in the aqueous phase and a light yellow in the ether phase.

The column was then treated with 0.1*M* KH_2PO_4–H_3PO_4, *p*H 2.1. Ten-ml. aliquots were placed on the column, and the corresponding 10-ml. effluents were collected and tested with KI. In this system, the "breakthrough" point is neatly indicated by the bleaching of the resin which occurs upon conversion of the hydroxyl form to the phosphate form. In this particular instance, the effluent including the breakthrough point gave a strong test for peroxides; the effluent samples immediately preceding and succeeding gave much weaker tests. Phosphate eluates from otherwise untreated Dowex 1 columns gave completely negative tests.

A test was also performed to investigate the possibility that peroxide accumulation in stored ether can be prevented by the inclusion of a small amount of the ion exchange resin. For this purpose, 500 ml. of C.P. ether was freed of peroxides by passing through a column of Dowex 1 (hydroxyl form). The peroxide-free ether was divided equally between two clear glass pressure bottles, which were placed side by side in the path of direct sunlight. One of the bottles contained 10 g. of Dowex 1 (hydroxyl form). At the intervals shown in Table I, the bottles were carefully opened without otherwise disturbing them, and 25-ml. aliquots were removed by rubber bulbed pipet and assayed for peroxide by the iodometric method of Reimers.[3] After the 7-day samples had been withdrawn, the bottles were temporarily closed and inverted twice, and the contents were re-sampled for peroxides. Table I indicates clearly the formation of peroxides in the stored ether, and the prevention of such accumulation by the incorporation of the anion exchanger. The somewhat irregular rate of formation of peroxides is probably due to daily variation in the amount of sunlight received; some of the included days were quite overcast.

It has been demonstrated[4–6] that H_2O_2 has some degrada-

(1) This work was performed under the auspices of the U. S. Atomic Energy Commission.

(2) Reagent Chemicals: American Chemical Society, Specifications 1955 (American Chemical Society, Washington, D. C.).

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tive effects on at least some ion exchange resins, and the possibility must be borne in mind that ether freed of peroxides as described above may contain trace contaminants rendering it unsuitable for certain specific usages, unless distilled. In actual test, the following residues were found after evaporation of 1 l. of ether, the final weighings being done after bringing to constant weight *in vacuo* at room temperature:

	Mg.
C.P. ether, peroxide-free, untreated with resin	1.4 (colorless)
C.P. ether, peroxide-free, mixed for 2 hr. at room temperature with 150 g. moist Dowex 1 (hydroxyl form)	4.2 (colorless)
C.P. ether, initially peroxide-rich, mixed with Dowex as above	47.6 (green-yellow)

(6) K. M. Saldadze and Z. G. Demonterik, Trans. Session on Applications of Ion Exchange Chromatography in Medicine and the Food Industries, Acad. Sci. U.S.S.R., Div. Chem. Sci., Commission on Chromatography (1957) (English trans. by Consultants Bureau, p. 96 (1958)].

It should be noted that this was an extreme test, in that the amount of peroxide present was such as nearly to saturate the capacity of the resin; such peroxide content will ordinarily be obtained only by deliberate ill handling, as in the experiment of Table I.

TABLE I

PREVENTION OF PEROXIDE ACCUMULATION IN STORED ETHER BY INCLUSION OF ANION EXCHANGE RESIN

Time of Standing in Sun (Days)	Milliequiv. Peroxide/L. Ether		Reduction Due to Dowex, %
	Without Dowex 1	With Dowex 1	
Initial	0.00	0.00	—
1	0.43	0.06	86
2	0.54	0.10	81
4	1.32	0.12	91
7	2.70	0.13	95
7 (after inverting)	2.69	0.05	98

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Communications TO THE EDITOR

The Presence of C_{20} Unsaturated Fatty Acids in Tall Oil

Sir:

There have been many investigations of the fatty acid constituents of tall oil, a mixture of resin acids, fatty acids, and neutral material, which is obtained by acidifying the black liquor skimmings of the sulfate process for the manufacture of pulp. Pine wood is used almost exclusively.

It is well known that the fatty acids of tall oil consist largely of oleic and linoleic acids although small amounts of stearic, palmitic, and conjugated linoleic acids are also present. A trace of linolenic acid is present in crude tall oil. Traces of myristic[1] and lignoceric[2] acids have been reported as being present in European oil. Palmitic and myristic acids could possibly be formed from oleic acid during the pulping.[3]

Most of the tall oil being produced in the South is by distillation fractionated to produce rosin and fatty acids. While working with the methyl esters of one type of distillate we observed that a small amount of a higher boiling fraction was obtained when the esters were fractionated through a laboratory column.

Vapor phase chromatography confirmed the presence of a fraction boiling higher than the known C_{18} acids. The methyl esters, free of rosin acids, occurring in about 12% concentration in the particular fraction we were examining, had a 20 min. retention time as compared to 13.5 min. for the C_{18} acids and 7.5 min. for palmitic acid. Helium was used as the carrier gas—30 ml./min. at 116.6 cm. absolute pressure at the column inlet and 76 cm. at the outlet. The column was 1/4 in. o.d. and 6 ft. long, packed with Dow-Corning high vacuum silicone grease supported on 60–100 mesh white Celite and maintained at 248°.

In order to study this fraction we esterified a large batch of distilled tall oil with methanol–sulfuric acid and removed the unesterified rosin acids by extracting with 1% sodium hydroxide. The recovered methyl esters of the fatty acids were fractionated at 1–2 mm. through a 2 × 48 in. vacuum jacketed column packed with protruded stainless steel packing. The first fractions were rich (37–61%) in conjugated acids, probably linoleic. As fractionation progressed the conjugated acids were slowly removed and they amounted to only 1% in the higher boiling fractions. A center cut of the higher boiling fraction had an iodine number of 213 and n_D^{30} 1.4677. The free acids recovered from a saponified sample had a neutralization equivalent of 307.5, n_D^{30} 1.4750 and an iodine number of 212. The methyl esters (18.8 g.) were hydrogenated in acetic acid at 60 lb. pressure using platinum oxide as the catalyst. Hydrogenation was rapid and complete, about 2.5 moles of hydrogen was absorbed. After filtering hot, the acetic acid was allowed to cool, thus recovering 10.8 g. of white crystals. One crystallization from ethanol in 95% yield yielded a product that melted at 46.5–47.5° (corr.). A reference sample of methyl arachidate melting at 46.6° did not lower the melting point of our sample. The remainder of the ester was removed from the acetic acid solution by adding water. This product was also nearly pure methyl arachidate as evidenced by the melting point and vapor phase chromatography data.

The saturated methyl esters were saponified and crystallized once from ethanol in 95% yield. The recovered acid had a melting point of 76° (corr.). A reference sample of arachidic acid did not lower the melting point. The neutralization equivalent was 312.9; calculated 312.5. From the iodine number, the amount of hydrogen absorbed, the refractive index, the boiling point of the methyl esters and the inability to obtain any crystallization of either the free acids or the methyl esters it appears that this higher boiling fraction is composed of approximately equal amounts of dienoic and trienoic nonconjugated C_{20} acids. From our fractionation data and vapor phase chromatography analysis we estimate there is approximately 1.4–1.7% unsaturated C_{20} acids in crude tall oil based on our analyses of the amounts present in the volatile fractions we have studied.

We believe this observation to be of special interest as, to the best of our knowledge, C_{20} unsaturated fatty acids of vegetable origin are not known to occur in such widely used and common source as the southern pine.[4,5]

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Received May 15, 1959

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(5) We wish to express our appreciation to Dr. H. G. Hunt for the chromatography data.