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Errata

The December 1959 issue of the JOURNAL contained two title pages for use in binding copies issued in 1959. These pages followed page 2108.

An error appears on these pages—"Volume 23" should read "Volume 24."

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, WAYNE STATE UNIVERSITY AND THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MAINE]

Reaction of the Steroidal Sapogenin Spiroketal System with Ethanedithiol[1]

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Ethanedithiol in the presence of boron trifluoride etherate reacts with the spiroketal system of steroidal sapogenins to form the corresponding furostane 26-ethylenethioketal. Desulfurization leads to the furostane which in the 5α series was transformed into cholestan-16β-ol. Structural formulas are proposed to explain these reactions.

The spiroketal ring system, characteristic of the steroidal sapogenins, was first recognized by Marker and Rohrmann[4] who observed its stability to most reagents which were not acidic. While the spiroketal grouping is opened[4,5] under the strongly acid conditions prevailing in the Clemmensen reduction, the ketone function of carbonyl-containing sapogenins can be removed readily[6] by the Wolff-Kishner reduction, including[7] Huang-Minlon's modification.[8] Subsequently, the formation of mercaptals and desulfurization with Raney nickel, introduced by Hauptmann in the steroid series,[9] was also employed with sapogenins and the required sapogenin mercaptals were prepared using zinc chloride,[10] hydrogen bromide[11] hydrogen chloride,[12] or perchloric acid[13] as the condensing agent without affecting the spiroketal moiety. In an attempt to utilize the boron trifluoride procedure[14] for the synthesis of certain steroidal sapogenin ethylenethioketals,[15] it was observed that reaction with the side chain had occurred since the characteristic infrared bands[16] associated with the spiroketal system had disappeared. In view of the importance of steroidal sapogenins in connection with the synthesis of steroid hormones[17] and the relative paucity of reactions which the spiroketal system undergoes,[18,19] we have undertaken a more detailed

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(3) Monsanto Predoctorate Research Fellow, 1955–1956.

(4) R. E. Marker and E. Rohrmann, *J. Am. Chem. Soc.*, **61**, 846 (1939).

(5) See also R. E. Marker and E. Rohrmann, *J. Am. Chem. Soc.*, **62**, 896 (1940).

(6) See for instance R. E. Marker, R. B. Wagner, P. R. Ulshafer, E. L. Wittbecker, D. P. J. Goldsmith, and C. H. Ruof, *J. Am. Chem. Soc.*, **69**, 2167 (1947).

(7) See C. Djerassi, H. Martinez, and G. Rosenkranz, *J. Org. Chem.*, **16**, 1278 (1951).

(8) Huang-Minlon, *J. Am. Chem. Soc.*, **71**, 3301 (1949).

(9) H. Hauptmann, *J. Am. Chem. Soc.*, **69**, 562 (1947).

(10) C. Djerassi, E. Batres, M. Velasco, and G. Rosenkranz, *J. Am. Chem. Soc.*, **74**, 1712 (1952); J. Romo, G. Stork, G. Rosenkranz, and C. Djerassi, *J. Am. Chem. Soc.*, **74**, 2918 (1952).

(11) G. Rosenkranz, M. Velasco, C. Djerassi, and F. Sondheimer, *J. Am. Chem. Soc.*, **75**, 4430 (1953).

(12) C. Djerassi, H. J. Ringold, and G. Rosenkranz, *J. Am. Chem. Soc.*, **76**, 5533 (1954).

(13) D. L. Klass, M. Fieser, and L. F. Fieser, *J. Am. Chem. Soc.*, **77**, 3829 (1955).

(14) L. F. Fieser, *J. Am. Chem. Soc.*, **76**, 1945 (1954).

(15) See C. Djerassi, T. T., Grossnickle, and L. B. High, *J. Am. Chem. Soc.*, **78**, 3166 (1956), footnote 34.

(16) R. N. Jones, E. Katzenellenbogen, and K. Dobriner, *J. Am. Chem. Soc.*, **75**, 158 (1953); C. R. Eddy, M. E. Wall, and M. K. Scott, *Anal. Chem.*, **25**, 266 (1953).

(17) For recent review see C. Djerassi, Proc. Fourth Internat. Congress Biochem., Vienna, September 1958, Symposium IV.

(18) See L. F. Fieser and M. Fieser, *Natural Products Related to Phenanthrene*, Reinhold Publishing Corp., New York, 1949, chapter VIII.

(19) For recent references see E. S. Wallis and R. S. Miner, *J. Org. Chem.*, **21**, 715 (1956); R. K. Callow and P. N. Massy-Beresford, *J. Chem. Soc.*, 4482 (1957).

examination of its behavior toward boron trifluoride etherate and certain mercaptans.

Tigogenin acetate (Ia) upon treatment with ethanedithiol or propane-1,3-dithiol in the presence of boron trifluoride etherate[14] furnished the sulfur-containing products IVa and IV, whose structure will be discussed below. Desulfurization of either substance with Raney nickel catalyst led to the sulfur-free product subsequently shown to be 5α-furostan-3β-ol acetate (VIIIa) which represented the key intermediate for all further work. The identical compound VIIIa could also be obtained from either diosgenin acetate (II) or hecogenin acetate (III) by the following routes, thus establishing the generality of this reaction and the fact that it involved only the spiroketal side chain. Condensation of diosgenin acetate (II) with ethanedithiol–boron trifluoride etherate yielded Va, which was desulfurized with Raney nickel catalyst to 5-furosten-3β-ol acetate (VII) and then hydrogenated in acetic acid solution with platinum oxide to 5α-furostan-3β-ol acetate (VIIIa). In the case of hecogenin acetate (III), it was interesting to determine whether the 12-keto function would complicate matters but the reaction with either ethanedithiol or propane-1,3-dithiol proceeded smoothly *via* the 12-mercaptals (VIa and VIb) and after desulfurization provided VIIIa. Sarsasapogenin acetate (5β, Ia) was converted to the compound eventually shown to be 5β-furostan-3β-ol acetate (5β, VIIIa) by an analogous series of reactions.

The analytical composition of the sulfur containing intermediates (IV, V, VI) as well as of the desulfurization products VII and VIIIa indicated the loss of one oxygen atom. The ether nature of the single oxygen atom derived from the spiroketal grouping was demonstrated as follows. The acetate VIIIa exhibited no hydroxyl absorption in the infrared and saponification gave the corresponding alcohol VIIIb which could be reacetylated to the starting acetate VIIIa. Oxidation of the alcohol VIIIb led to the ketone VIIIc which was reduced by the Huang-Minlon modification[8] of the Wolff-Kishner procedure to 5α-furostane (VIIId), which did not exhibit any hydroxyl or carbonyl absorption in the infrared and did not possess any active hydrogen atom (Zerewitinoff determination). The identical ether VIIId could also be obtained by treatment of deoxytigogenin (Ic)[20] with ethanedithiol–boron trifluoride etherate, followed by desulfurization or most directly by transforming tigogenone (Ib)[21] into the 3-ethylenethioketal IVc and then desulfurizing.

In order to determine the structure of the ether ring and to establish that no skeletal rearrangement had occurred, it was necessary to accomplish interconversion with a known steroid and ether cleavage experiments appeared to offer the most direct avenue. For this purpose the ether subsequently shown to be VIIId (5α-furostane) was selected and a variety of reagents were examined, of which the following proved unsatisfactory in initial experiments: boron trifluoride etherate–acetic acid,[22] zinc chloride–acetic anhydride,[23] hydrogen iodide,[24] or hydrogen bromide–acetic anhydride.[25] On the other hand, treatment of the ether VIIId with *p*-toluenesulfonic acid in acetic anhydride[26] led to an oily mixture of isomeric monounsaturated acetates ($C_{29}H_{48}O_2$). Careful chromatography yielded a small amount of a crystalline isomer which was shown to be Δ^{23}-cholesten-16β-ol acetate (IX) since ozonolysis furnished isovaleraldehyde and (after treatment with alkaline hydrogen peroxide and acidification) 16β-hydroxybisnorallocholanic 22 → 16 lactone (X).[27] Catalytic hydrogenation led to the acetate XIa, which was hydrolyzed by means of lithium aluminum hydride to cholestan-16β-ol (XIb)[28] and further oxidized to cholestan-16-one (XII). The identical sequence of reactions could be performed with the oily ether cleavage product which also gave some of the crystalline alcohol XIb and thence the ketone XII.

The conversion of the ethanedithiol–boron trifluoride etherate condensation products *via* the ether VIIId to cholestan-16β-ol (XIb) demonstrates that no skeletal rearrangement was involved in ether formation and furthermore, that one terminus of the ether ring must be at C-16. The isolation of a 16β-ol was of some mechanistic importance since if ether formation had proceeded by a displacement reaction at C-16, a 16α-hydroxy derivative would have resulted almost certainly.

There now remained the question regarding the other point of attachment of the ether ring. Mechanistically, initial attack by sulfur could be assumed to proceed at C-22(A) to give an intermediate such as B. Displacement by the second sulfur atom on C-22 of B and eventual ether ring closure would lead to a 16,26-oxide[29] (C) and such a formulation was originally favored by us. While the olefin IX is apparently only a minor constituent of the iso-

(20) (a) R. E. Marker and D. L. Turner, *J. Am. Chem. Soc.*, **63**, 767 (1941); (b) J. Romo, M. Romero, C. Djerassi, and G. Rosenkranz, *J. Am. Chem. Soc.*, **73**, 1528 (1951).

(21) W. A. Jacobs and E. E. Fleck, *J. Biol. Chem.*, **88**, 545 (1930).

(22) G. F. Hennion, H. D. Hinton, and J. A. Nieuwland, *J. Am. Chem. Soc.*, **55**, 2857 (1933).

(23) C. L. Wilson, *J. Chem. Soc.*, 48 (1945).

(24) H. Stone and H. Shechter, *J. Org. Chem.*, **15**, 491 (1950).

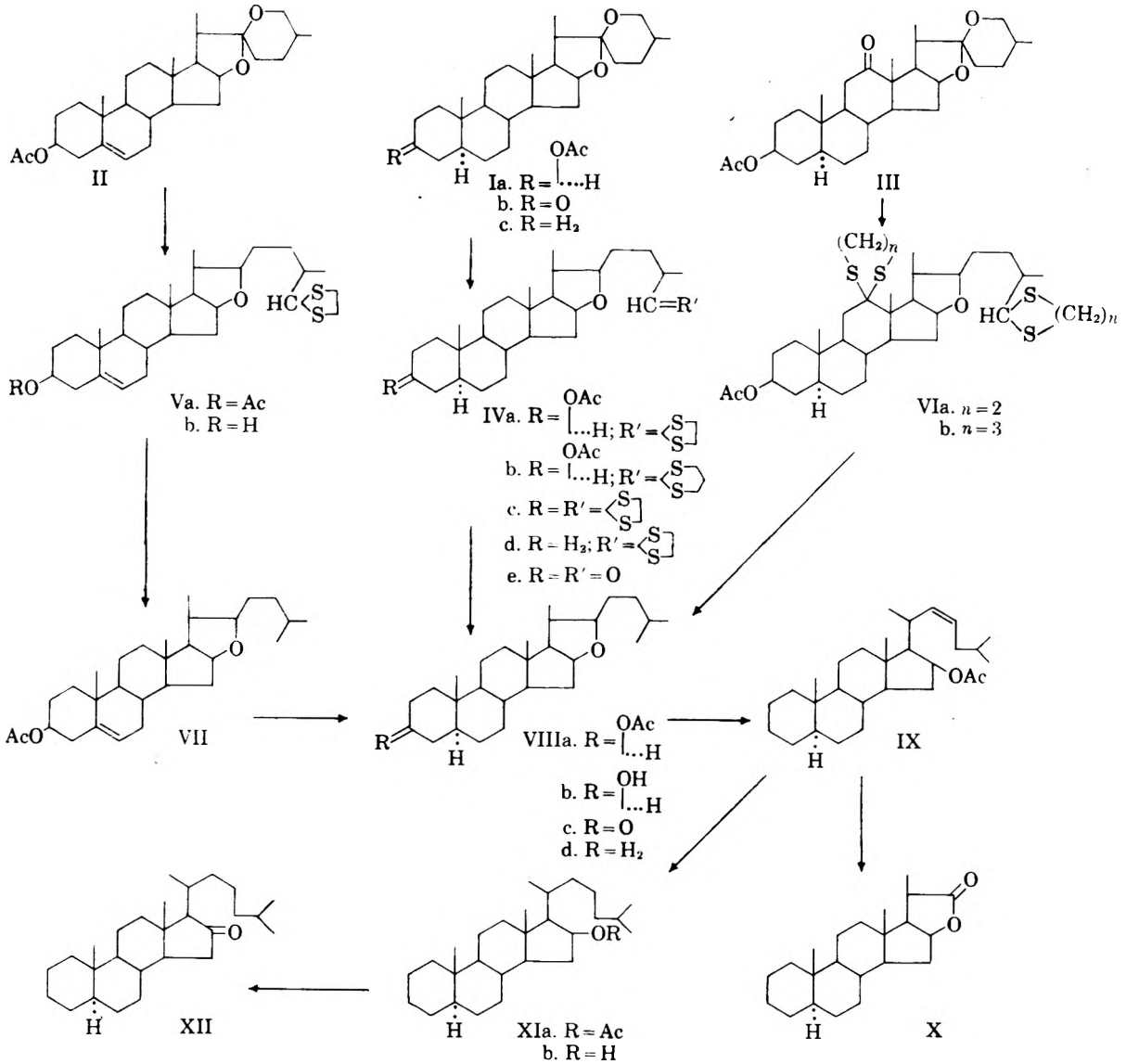
(25) R. B. Turner, V. R. Mattox, L. L. Engel, B. McKenzie, and E. C. Kendall, *J. Biol. Chem.*, **166**, 345 (1946).

(26) M. N. Huffman and M. H. Lott, *J. Biol. Chem.*, **172**, 789 (1948); L. Ruzicka, W. Baumgartner, and V. Prelog, *Helv. Chim. Acta*, **32**, 2069 (1949).

(27) R. Tschesche and A. Hagedorn, *Ber.*, **68**, 1412 (1935).

(28) I. Scheer and E. Mosettig, *J. Am. Chem. Soc.*, **77**, 1820 (1955).

(29) The oxide could also have been eight-membered by terminating at C-25 since the intimate steps (*e.g.*, initial formation of an intermediate Δ^{25}-olefin) involved in this ether ring closure are not known.



meric mixture of unsaturated acetates produced in the ether cleavage, its formation from C could be rationalized readily by assuming a transannular hydrogen transfer (D) which is known to occur frequently in medium-sized rings.

At this stage of the investigation, our attention was directed[30] to the fact that structures such as E had not been excluded as possible representations for the products of the boron trifluoride–catalyzed reaction of ethanedithiol and steroidal sapogenins. A substance of this type could be formed by attack of the second sulfur atom of B at C-26[31] in which case the desulfurization products (VII, VIII) would be furostane derivatives. Such 16,22-oxides were prepared[32a] originally in the steroidal 5β-series, but subsequently[32b] the corresponding 5α-isomer (VIIIb) has also been synthesized by an unambiguous route. Through the kind cooperation of Dr. E. Mosettig of the National Institutes of Health, samples of authentic 5α- and 5β-furostan-3β-ol were secured and were found to be identical with the corresponding specimens derived from the desulfurization of the ethanedithiol condensation products.

The identification of the desulfurization products (VIII) as 16,22-oxides demonstrates that the reaction of ethanedithiol (or propane-1,3-dithiol) with the steroidal spiroketal side chain in the presence of boron trifluoride etherate proceeds by formation of a new sulfur-containing ring (*e.g.*, IVa).

Very recently,[33] there has been suggested and

(30) We acknowledge with pleasure a profitable discussion on the subject of this paper with Prof. D. H. R. Barton, Imperial College of Science and Technology, London.

(31) Ring closure at C-25 rather than at C-26 (*e.g.*, E) was not excluded since the reaction might conceivably proceed by addition of the mercaptan to a Δ^{25}-olefin intermediate. Dimeric structures were eliminated by Rast molecular weight determinations.

(32) (a) I. Scheer, R. B. Kostic, and E. Mosettig, *J. Am. Chem. Soc.*, **77**, 641 (1955); (b) G. Sato, H. G. Latham, and I. Scheer, *J. Org. Chem.*, **21**, 689 (1956).

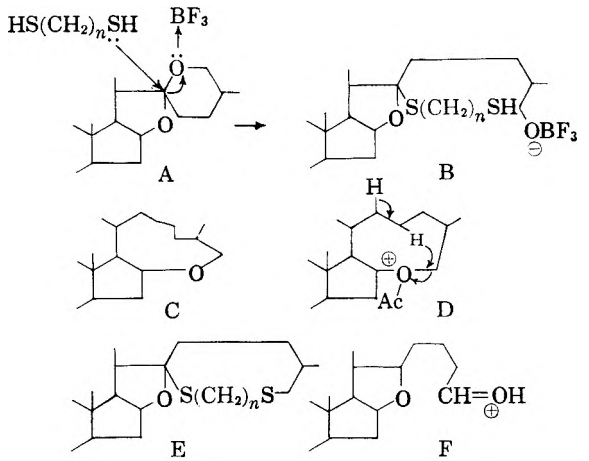
(33) R. B. Woodward, F. Sondheimer and Y. Mazur, *J. Am. Chem. Soc.*, in press. We are greatly indebted to Professor Woodward for calling this work to our attention and to Dr. F. Sondheimer for providing experimental details prior to publication.

TABLE I

Product	Yield, %[a]	M.P., °C.	$[\alpha]_D$	Empirical Formula	Analysis					
					Calcd.			Found		
					C	H	S	C	H	S
5α-furostan-3β-ol acetate 26-ethylenethioketal (IVa)[b]	70	123–124.5	−7°	$C_{31}H_{50}O_3S_2$	69.63	9.43	11.98	69.33	9.24	12.19
5β-furostan-3β-ol acetate 26-ethylenethioketal (5β, IVa)	69	121–123	+1.8°	$C_{31}H_{50}O_3S_2$	69.63	9.43	11.98	69.52	9.30	12.01
5α-furostan-3β-ol acetate 26-trimethylenethioketal (IVb)	38	130.5–132	−10°	$C_{32}H_{52}O_3S_2$	70.04	9.55	11.68	70.09	9.69	11.94
5α-furostane 3,26-bisethylene-thioketal (IVc)	60	159–160.5	+11°	$C_{31}H_{50}OS_4$	65.68	8.89	22.62	66.01	8.90	22.73
5α-furostane 26-ethylenethioketal (IVd)	54	96.5–98	+8°	$C_{29}H_{48}OS_2$	73.06	10.15	13.45	73.12	10.25	13.59
5-furosten-3β-ol acetate 26-ethylenethioketal (Va)	55	140–142	−31°	$C_{31}H_{48}O_3S_2$	69.89	9.08	12.04	69.51	9.19	12.81
5-furosten-3β-ol 26-ethylenethioketal (Vb)[c]	80	148–149	−22°	$C_{29}H_{46}O_2S_2$	70.98	9.45	13.07	70.62	9.84	12.60
5α-furostan-3β-ol acetate 12,26-bisethylenethioketal (VIa)	75	165–166.5	+39°	$C_{33}H_{52}O_3S_4$	63.46	8.33	20.05	63.97	8.57	19.94
5α-furostan-3β-ol acetate 12,26-bistrimethylenethioketal (VIb)	60	226–227.5	+24°	$C_{35}H_{56}O_3S_4$	64.64	8.68	19.72	63.93	8.27	19.29

[a] After recrystallization. [b] The substance exhibited λ_{max}^{EtOH} 239 mμ (log ε 3.11) and λ_{max}^{EtOH} 227 mμ (log ε 3.08). [c] Obtained from Va by saponification (18 hr., 20°) with 5% methanolic potassium hydroxide or by heating for 25 hr. under reflux with ethanol-water–concd. hydrochloric acid (6:1:1).

experimental evidence presented for a new mechanism for the acid-catalyzed isomerization of the steroidal sapogenin side chain which is postulated to proceed *via* F–the conjugate acid of the aldehyde of a dihydrosapogenin. Consequently, the possibility existed that our boron trifluoride-ethanedithiol reaction simply involved capture of this aldehyde intermediate in the form of its thioketal (*e. g.* IVa, V, VI). This was actually shown to be the case by oxidizing dihydrotigogenin by the reported procedure[33] to the 3-keto-26-aldehyde IVe and treating the crude product directly with ethanedithiol in the presence of boron triflouride or a trace of perchloric acid (known[13] not to affect the sapogenin side chain). In each case, there was obtained the identical 3,26-bis-thioketal IVc, which had already been isolated above in one step from tigogenone (Ib) and ethanedithiol-boron trifluoride. There remains no question, that the structures of our condensation products are represented by IVa, V and VI and that the formation of these substances constitutes additional support for the Woodward-Sondheimer-Mazur mechanism[33] of steroidal sapogenin side chain isomerization.



EXPERIMENTAL[34]

Reaction of steroidal sapogenins with ethanedithiol and propane-1,3-dithiol in the presence of boron trifluoride. Two typical procedures will be given below while the pertinent physical constants and analytical results are summarized in Table I.

A mixture of 4.2 g. of tigogenin acetate (Ia), 8.65 g. of ethanedithiol, and 7.6 cc. of boron trifluoride etherate was left at room temperature for 2 hr.,[35] diluted with benzene, washed with *N* sodium hydroxide and water, dried, and evaporated *in vacuo*. Crystallization from acetone furnished 3.5 g. of the adduct IVa (see Table I).

The dark colored solution which formed upon mixing 1.0 g. of hecogenin acetate (III) with 2.7 g. of propane-1,3-dithiol[36] and 2.5 cc. of boron trifluoride etherate was diluted with much benzene after 1 hr. Extraction with alkali and water, followed by drying and evaporation *in vacuo* left an oily residue which was chromatographed in 1:1 hexane-benzene solution on 30 g. of alumina. Elution with benzene provided 1.18 g. of crystalline product (VIb), m.p. 225–227° (see Table I).

Substitution of β-mercaptoethanol for ethanedithiol yielded only unchanged sapogenin and this also applied to use of β-mercaptoethanol in conjunction with aluminum chloride or zinc chloride.

(34) Melting points were determined on the Kofler block. Unless noted otherwise, rotations were measured in chloroform solution. We are indebted to Mrs. Dolores Phillips for the infrared measurements and to Dr. A. Bernhardt, Mülheim, Germany, for the microanalyses.

(35) All of the tigogenin acetate dissolved only after 30 min.

(36) J. R. Meadow and E. E. Reid, *J. Am. Chem. Soc.*, **56**, 2177 (1934); S. D. Simpson, *Can. J. Research*, **25B**, 20 (1947).

5α-Furostane 3,26-bisethylenethioketal (IVc) via dihydrotigogenin. A solution of dihydrotigogenin[37] (1.59 g.) in 100 ml. of benzene containing 10 ml. of glacial acetic acid was cooled in ice and treated over a 15 min. period with a solution composed of sodium dichromate (10 g.), concentrated sulfuric acid (2.5 ml.) and 60% acetic acid (140 ml.). Stirring was continued with cooling for an additional 1.75 hr. Excess oxidizing agent was then reduced with aqueous ferrous sulfate. After separating the benzene solution, the aqueous mixture was extracted with ether and the combined solvents were washed repeatedly with water. The straw colored oily residue, obtained by removing the dry (sodium sulfate) solvents *in vacuo*, weighed 1.5 g.

The crude 3-keto-26-aldehyde (0.70 g.) was treated with 3 ml. of ethanedithiol and one drop of perchloric acid (70–72%). After 2 hr., the mixture was diluted with ether and washed successively with 2*N* sodium hydroxide and water. Removal of solvent *in vacuo* afforded a straw colored oil. Chromatography on Merck activated alumina and elution with petroleum ether-benzene (1:4) gave 105 mg. of crystalline 5α-furostane 3,26-bisethylenethioketal melting at 158–160°. Recrystallization from ethyl acetate afforded 50 mg. of colorless needles, m.p. 159–160.5°. The product (IVc) was identical (mixture melting point and infrared comparison) with a specimen prepared by reacting tigogenone with ethanedithiol in the presence of boron trifluoride etherate (Table I).

5α-Furostan-3β-ol acetate (VIIIa). (*a*) *By desulfurization of 5α-furostan-3β-ol acetate 12,26-bisethylenethioketal* (VIa). A solution of 1.0 g. of the thioketal VIa in 100 cc. of ethanol was heated under reflux for 4 hr. with 14 g. of W-4 Raney nickel catalyst.[38] Filtration of the catalyst, concentration of the filtrate and chilling afforded 0.53 g. (74%) of colorless needles, m.p. 82–84.5°. Further recrystallization from ethanol led to the analytical sample, m.p. 83.5–84.5°, $[\alpha]_D$ −14°, $\lambda_{max}^{CHCl_3}$. 5.75 and 7.90 μ.

Anal. Calcd. for $C_{29}H_{48}O_3$: C, 78.32; H, 10.88. Found: C, 78.32; H, 10.82.

The corresponding 12-trimethylenethioketal VIb was desulfurized under the same conditions in 67% yield to 5α-furostan-3β-ol acetate (VIIIa).

In one experiment, where W-2 Raney nickel[38] was employed and the ratio between VIa and catalyst was only 1:5, there was isolated in about 60% yield a monothioketal which proved to be different from 5α-furostan-3β-ol acetate 26-ethylenethioketal (IVa) and which is, therefore, assigned the structure 5α-furostan-3β-ol acetate 12-ethylenethioketal. The substance crystallized from aqueous acetone as colorless plates, m.p. 155–157°, $[\alpha]_D$ +30°, $\lambda_{max}^{CHCl_3}$ 5.78 and 7.95 μ.

Anal. Calcd. for $C_{31}H_{50}O_3S_2$: C, 69.63; H, 9.43; S, 11.98. Found: C, 69.91; H, 9.53; S, 11.62.

(*b*) *By desulfurization of 5α-furostan-3β-ol acetate 26-trimethylenedithioketal* (IVb). A solution of 0.2 g. of the acetate IVb in 30 cc. of ethanol was heated under reflux for 2 hr. with 2 g. of W-4 Raney nickel catalyst and processed in the usual manner to provide 67% of 5α-furostan-3β-ol acetate (VIIIa), m.p. 82–83.5°.

(*c*) *By desulfurization of 5α-furostan-3β-ol acetate 26-ethylenethioketal* (IVa). Desulfurization was accomplished by refluxing the acetate (1.5 g.) for 18 hr. in 150 ml. of ethanol with 12 g. of W-4 Raney nickel. Isolation and crystallization from ethanol afforded 0.78 g. (75%) of colorless crystalline product, m.p. 80–83°.

The analogous *5β-furostan-3β-ol acetate* (5β, VIIIa) was prepared by an identical procedure employing 5β-furostan-3β-ol acetate 26-ethylenethioketal (5β, IVa) (0.8 g.), ethanol (75 ml.), and W-4 Raney nickel (6 g.). The product crystallized as colorless needles from ethanol; weight 0.5 g., m.p. 80–82°. Recrystallization from ethanol gave a pure sample, m.p. 82–83°, $[\alpha]_D$ −4.5°.

Anal. Calcd. for $C_{29}H_{48}O_3$: C, 78.32; H, 10.88. Found: C, 77.93; H, 11.76.

(*d*) *By hydrogenation of 5-furosten-3β-ol acetate* (VII). The desulfurization of 5-furosten-3β-ol acetate 26-ethylenethioketal (Va) proceeded in 60% yield when conducted in boiling ethanol (2.5 hr.) with eight times the weight of W-2 Raney nickel.[38,39] Recrystallization from ethanol gave 5-furosten-3β-ol acetate (VII), m.p. 130–132°.

Anal. Calcd. for $C_{29}H_{46}O_3$: C, 78.68; H, 10.47. Found: C, 78.74; H, 10.38.

The above unsaturated ether VII (1.0 g.) was hydrogenated over a 2-hr. period in 100 cc. of glacial acetic acid with 0.2 g. of platinum oxide catalyst using 3 atm. of hydrogen. Filtration of the catalyst, evaporation of the solvent, and recrystallization from ethanol yielded 0.8 g. of 5α-furostan-3β-ol acetate (VIIIa), m.p. 78–81°.

In procedures *b–d* compound VIIIa was identified by mixture melting point and infrared comparison with the specimen produced *via* route *a*.

5α-Furostan-3β-ol (VIIIb). Saponification of the acetate VIIIa was accomplished by heating a solution of 1.0 g. of VIIIa in 60 cc. of 5% methanolic potassium hydroxide under reflux for 1 hr., concentrating the solution to one-half its volume and cooling. Filtration provided 0.8 g. of the alcohol VIIIa (m.p. 147–149°), which was recrystallized from hexane whereupon the melting point was raised to 148.5–150°, $[\alpha]_D$ −10°.

Anal. Calcd. for $C_{27}H_{46}O_2$: C, 80.54; H, 11.52. Found: C, 80.45; H, 11.34.

Conversion of 5β-furostan-3β-ol acetate (5β, VIIIa) (0.3 g.) to *5β-furostan-3β-ol* (5β, VIIIb) (0.2 g.) was carried out in similar fashion. An analytical sample recrystallized from methanol exhibited a melting point of 136–138°, $[\alpha]_D$ −4.1°.

Anal. Calcd. for $C_{27}H_{46}O_2$: C, 80.54; H, 11.52. Found: C, 80.36; H, 11.41.

The product was identical (mixture melting point and infrared comparison) with an authentic sample of 5β-furostan-3β-ol (5β, VIIIb).[32a]

A mixture melting point determination with VIIIb and an authentic sample of 5α-furostan-3β-ol (VIIIb)[32b] was undepressed.

Acetylation of a sample of the alcohol VIIIb with boiling acetic anhydride–pyridine led to the original acetate VIIIa, m.p. 82–84.5°.

5α-Furostan-3-one (VIIIc). The oxidation of 0.5 g. of the alcohol VIIIb was carried out in 10 cc. of glacial acetic acid with 50 mg. of chromium trioxide dissolved in 5 cc. of 80% acetic acid. Dilution with water, extraction with ether, and purification by filtration through alumina and recrystallization from aqueous ethanol led to colorless plates of the ketone VIIIc, m.p. 134–135°, $[\alpha]_D$ +15°, $\lambda_{max}^{CHCl_3}$ 5.84 μ.

Anal. Calcd. for $C_{27}H_{44}O_2$: C, 80.94; H, 11.07. Found: C, 80.24; H, 11.64.

5α-Furostane (VIIId). (*a*) *By desulfurization of 5α-furostane 26-ethylenthioketal* (IVd). The desulfurization of 0.3 g. of IVd (see Table I) in 100 cc. of ethanol was performed in the usual manner (2 hr.) with 3 g. of W-4 Raney nickel and led in 87% yield to 5α-furostane, which crystallized from ethanol as colorless leaflets, m.p. 95–96°, $[\alpha]_D$ −9°, no infrared hydroxyl or carbonyl absorption.

Anal. Calcd. for $C_{27}H_{46}O$: C, 83.87; H, 11.99. Found: C, 83.91; H, 11.91; active hydrogen, 0.00.

(*b*) *By desulfurization of 5α-furostane 3,26-bisethylenethioketal* (IVc). The desulfurization of the thioketal IVc (see Table I) was conducted in the usual manner except that an extended reflux time (30 hr.) was necessary for optimum yields (69–76%).

(*c*) *By Wolff-Kishner reduction of 5α-furostan-3-one*

(37) R. E. Marker and E. Rohrmann, *J. Am. Chem. Soc.*, **61**, 1516 (1939).

(38) A. A. Pavlic and H. Adkins, *J. Am. Chem. Soc.*, **68**, 1471 (1946).

(39) With W-4 Raney nickel, some reduction of the 5,6-double bond was also observed.

(VIIIc). A mixture of 70 mg. of the ketone VIIIc, 70 mg. of potassium hydroxide, 1 cc. of triethylene glycol, and 0.1 g. of 85% hydrazine hydrate was heated for 3 hr. at 120–130°, the condenser was removed, the temperature raised to 195° whereupon refluxing was continued for 3.5 hr. Dilution with water, extraction with ether, and purification of the ether extract by chromatography on acid-washed alumina (hexane elution) followed by recrystallization from ethanol afforded 40 mg. of the ether VIIId, m.p. 92.5–94°, undepressed upon admixture with the specimens prepared according to *a* or *b*. The infrared spectra of all three samples were identical.

Ether cleavage of 5α-furostane (VIIId). A solution of 950 mg. of the ether VIIId and 500 mg. of *p*-toluenesulfonic acid monohydrate in 50 cc. of acetic anhydride was heated under reflux for 30 min. and then poured unto ice. After standing for 5 hr., the product was extracted with ether, washed until neutral, dried, and evaporated to yield 1.05 g. of a pale orange colored gum. Chromatography on 100 g. of Merck acid-washed alumina and elution with hexane gave 570 mg. of unreacted ether VIIId, followed by 490 mg. of a heavy, colorless oil which was eluted partly by hexane and partly by hexane-benzene mixtures (9:1). For analysis, a sample of the oil was rechromatographed and distilled at 180° and 0.005 mm.; yellow color with tetranitromethane, $\lambda_{max}^{CHCl_3}$ 5.78 and 7.95 μ.

Anal. Calcd. for $C_{29}H_{48}O_2$: C, 81.25; H, 11.29; O, 7.46. Found: C, 80.74; H, 11.05; O, 7.99.

Further elution with hexane-benzene (4:1) provided 75 mg. of crystals, which were recrystallized from ethanol to give an analytical sample of Δ^{23}-cholesten-16β-ol acetate (IX), m.p. 87–90°, $[\alpha]_D$ +18°, $\lambda_{max}^{CHCl_3}$ 5.77 and 7.90 μ.

Anal. Calcd. for $C_{29}H_{48}O_2$: C, 81.25; H, 11.29. Found: C, 81.08; H, 10.94.

When the ether cleavage was conducted with anhydrous *p*-toluenesulfonic acid (first heated at 100° and 40 mm. and subsequently distilled at a bath temperature of 200° and 0.005 mm.) and the time prolonged to 45 min., the results were substantially the same except that the amount of unreacted starting material was reduced and nearly 70% of oily, unsaturated acetate could be isolated.

Ozonolysis of Δ^{23}-cholesten-16β-ol acetate (IX). Ozone was passed for 15 min. at −80° through a solution of 119 mg. of the olefin IX in 2 cc. of methylene chloride and the solvent was then removed cautiously *in vacuo*. Water (20 cc.) was added and the mixture was steam distilled into a suspension of 2,4-dinitrophenylhydrazine in aqueous sulfuric acid. The distillate was extracted with benzene and the benzene solution passed through a short column of alumina. The combined benzene eluates were evaporated to give 35 mg. of crude, yellow 2,4-dinitrophenylhydrazone which was rechromatographed on alumina, eluted with hexane-benzene (2:1) and recrystallized from aqueous acetone, m.p. 122–124°. The melting point was depressed by over 30° upon admixture with acetone 2,4-dinitrophenylhydrazone but was undepressed when mixed with authentic isovaleralde hyde 2,4-dinitrophenylhydrazone (lit.,[40] m.p. 123°). The infrared spectra of the two samples were identical.

The residue from the stream distillation was heated for 30 min. with 10 cc. of 10% sodium hydroxide and 3 cc. of 30% hydrogen peroxide. After an additional hour at room temperature, the mixture was acidified, extracted with chloroform, and the chloroform extracts washed with sodium bicarbonate solution and water, dried, and evaporated. Chromatography on 3 g. of Merck acid-washed alumina, elution with hexane-benzene (1:1) and recrystallization from aqueous ethanol provided 13 mg. of 16β-hydroxybisnorallocholanic 22 → 16 lactone (X),[27] m.p. 198–199°, with sublimation and crystal change from needles to very fine hair-like crystals at 160°, $\lambda_{max}^{CHCl_3}$ 5.66 μ. Identity with an authentic specimen[41] was established by mixture melting point determination and infrared comparison.

Hydrogenation of Δ^{23}-cholesten-16β-ol acetate (IX). Reduction of 54 mg. of the olefin IX in 5 cc. of acetic acid at 29.5° and 1 atm. of hydrogen with 8 mg. of platinum oxide resulted in the uptake of 3.19 cc. (1.01 equivalents) of hydrogen within 4 min. After 10 min., the catalyst was filtered, the solvent was evaporated, and the residue crystallized twice from ethanol to provide 30 mg. of cholestan-16β-ol acetate (XIa), m.p. 116–117°, $[\alpha]_D$ +63°. The analytical sample was lost in transit but characterization was completed by conversion to XIb and XII.

The above acetate was converted in 90% yield to *cholestan-16β-ol* (XIb) by heating for 45 min. with an ethereal solution of lithium aluminum hydride. Recrystallization from aqueous methanol gave the analytical sample, m.p. 110–113°, then resolidifying and melting at 120–120.5°, $[\alpha]_D$ +30°. The mixture melting point with an authentic sample[28,42] was undepressed and the infrared spectra were identical.

For further identification, 9.7 mg. of cholestan-16β-ol (XIb) was oxidized in 0.5 cc of acetone with a few drops of 8*N* chromic acid–sulfuric acid–water solution[43] and after 2 min. the resulting cholestan-16-one (XII) was isolated by ether extraction and recrystallized from aqueous methanol, m.p. 94–95°, $\lambda_{max}^{CHCl_3}$ 5.75 μ, strong negative single Cotton effect typical[44] of 16-keto steroids (*c*, 0.09 in methanol, trough at $[\alpha]_{320}$ −2900°, peak at $[\alpha]_{277.5}$ +3100°). The infrared spectrum was identical with that of an authentic sample prepared by oxidation of cholestan-16β-ol.[28,42]

Anal. Calcd. for $C_{27}H_{46}O$: C, 83.87; H, 11.99. Found: C, 83.91; H, 12.06.

When the hydrogenation was performed with the oily unsaturated acetate obtained in the ether cleavage and the crude product saponified (using lithium aluminum hydride) followed by chromatography, there was isolated cholestan-16β-ol (XIb) as well as two isomers, m.p. 114–115° (depressed to 85–110° upon admixture with cholestan-16β-ol) and m.p. 143–145°. Unfortunately insufficient material was available for further work but one of these substances may represent the expected "reverse" ether cleavage product with the oxygen atom in the side chain.

Anal. Calcd. for $C_{27}H_{48}O$: C, 83.43; H, 12.45; O, 4.12. Found: sample, m.p. 114–115°: C, 82.95; H, 12.15; O, 4.59; sample, m.p. 143–145°: C, 83.22; H, 12.31; O, 4.18.

DETROIT, MICH.
ORONO, ME.

(40) S. M. McElvain *The Characterizati of Organic Compounds*, MacMillan Co., New York, 1953, p. 207.

(41) We are greatly indebted to Dr. Hans Hirschman, Western Reserve School of Medicine for this sample.

(42) We are grateful to Dr. Irving Scheer, National Institutes of Health, for this specimen.

(43) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, **39** (1946).

(44) C. Djerassi, W. Closson, and A. E. Lippman, *J. Am. Chem. Soc.*, **78**, 3163 (1956); C. Djerassi, R. Riniker, and B. Riniker, *J. Am. Chem. Soc.*, **78**, 6362 (1956).

[CONTRIBUTION FROM THE DEPARTMENT OF PATHOLOGY, THE GEORGETOWN UNIVERSITY MEDICAL CENTER]

Hypotensive Agents. X. 3-Azabicyclo[3.3.0]octane Derivatives[1,2]

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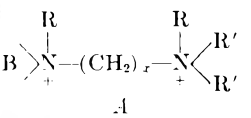
The investigation of various nitrogen heterocycles for use in the formation of symmetrical and unsymmetrical bis-ammonium salts for screening as hypotensive agents demonstrated dramatic changes in activity with variation in ring bridging. In the bicyclic rings derived from cyclohexane a change in the points of attachment of the second ring from the 1,2 positions (isoindole or 2-azabicyclo[4.3.0]nonane) to the 1,3 positions (3-azabicyclo[3.3.1]nonane) resulted in almost complete loss of hypotensive activity. Accordingly, we have investigated the effect of changing the points of attachment to the cyclopentane ring. *N*-Alkyl and *N*-dialkylaminoalkyl imides have been synthesized from *cis*-1,2-cyclopentane dicarboxylic anhydride and reduced to 3-azabicyclo[3.3.0]octanes. On comparison of the bis-quaternary salts with previously reported derivatives of the 1,3-anhydride, 3-azabicyclo[3.2.1]octane, which were very potent as hypotensive agents, significant loss of activity was not observed in the present series.

For many years we have been concerned with the synthesis of fused ring bi-and tricyclic nitrogen heterocycles for use as one or both of the terminal groups in the preparation of *alpha, omega* symmetrical and unsymmetrical bis-ammonium salts for screening in our hypertension chemotherapy program. Among the theories and methods advocated for the chemotherapeutic treatment of hypertensive disease the two most important have involved, at the extremes, emphasis on ganglioplegic agents and centrally acting agents. The pendulum of emphasis on the most desirable of either type of these agents for such use has vacillated frequently in the past decade. This shifting emphasis has probably been largely influenced by the therapeutic limitations of the chemical agents available from time to time.

In surveys of large groups of symmetrical[5-7] and unsymmetrical[8] bis-ammonium salts hypotensive activity has been encountered widely in both types. In the symmetrical types maximal therapeutic effectiveness has been generally attained when the terminal groups are small aliphatic radicals (hexamethonium hexane-1,6-bistrimethylammonium cation) or small heterocycles (pentolinium, pentane-1,5-bis-*N*-methyl pyrrolidinium cation) in which the onium centers are separated by a 5 or 6 membered polymethylene chain.

On the contrary, extensive studies by Cavallito and associates[8-11] as well as our group[12] have shown that the most desirable structure therapeutically, known at this time, in the unsymmetrical bis-ammonium type is represented by structure A.



A

In this general structure optimal effectiveness (as judged by the criteria of therapeutic ratio, potency, toxicity, duration of action, and therapeutic effectiveness *in vivo*) was usually encountered when x was 2 or 3, R methyl or ethyl (generally preferably methyl), R′ methyl or ethyl or small heterocycles such as morpholine, pyrrolidine, or piperidine (again generally preferably methyl), and B the residue of a small mono, di or tricyclic ring (in most cases preferably saturated).

While this simple structure-activity correlation is generally true, subtle and therapeutically significant differences in effectiveness have been brought about by relatively small changes in the basic structure. Changes in structure that affect therapeutic effectiveness comprise substitution on the ring, changing the bridging in the ring (thus changing its size and shape), length of the side chain, size and shape of end groups and quaternizing group.

In all of our past investigations concerning modification of the size and ring bridging (shape) of the terminal amine, hypotensive activity from moderate to excellent, in animals and man, was found in the following ring systems: 3-azabicyclo[3.2.1]-octane,[13] I, 1,8,8-trimethyl-3-azabicyclo[3.2.1]-

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(4) Present address: National Institutes of Health, Bethesda, Md.

(5) W. D. M. Paton and E. J. Zaimis, *Brit. J. Pharmacol*, **4**, 381 (1949).

(6) C. J. Cavallito, A. P. Gray, and E. E. Spinner, *J. Am. Chem. Soc.*, **76**, 1862 (1954).

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(10) A. P. Gray, E. E. Spinner, D. C. Schlieper, and C. J. Cavallito, *J. Am. Chem. Soc.* **77**, 3533 (1955).

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(12) L. M. Rice, C. H. Grogan, and E. E. Reid, *J. Am. Chem. Soc.*, **75**, 4911 (1953).

(13) C. H. Grogan and L. M. Rice, *J. Org. Chem.*, **22**, 1223 (1957).

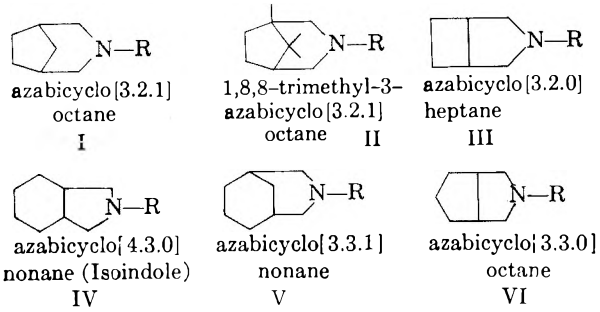
TABLE I

N-ALKYL-3-AZABICYCLO[3.3.0]OCTANE-2,4-DIONES

Alkyl	Formula	B.P., °C.	Mm.	Analyses, %[b] Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	n_D^{20}
Methyl	$C_8H_{11}NO_2$	144–148	29.0	62.73	62.95	7.24	7.05	9.15	9.22	1.5026[a]
Ethyl	$C_9H_{13}NO_2$	68–72	0.1	64.65	64.73	7.84	7.71	8.38	8.09	1.4933
Propyl	$C_{10}H_{15}NO_2$	68–72	0.05	66.27	66.60	8.34	8.10	7.73	7.79	1.4917
Butyl	$C_{11}H_{17}NO_2$	84–88	0.1	67.66	67.83	8.78	8.63	7.17	7.10	1.4875
Amyl	$C_{12}H_{19}NO_2$	86–94	0.08	68.86	68.80	9.15	8.98	6.69	6.54	1.4864
Hexyl	$C_{13}H_{21}NO_2$	90–95	0.05	69.92	69.89	9.48	9.30	6.27	6.37	1.4855
Heptyl	$C_{14}H_{23}NO_2$	103–107	0.07	70.85	70.99	9.77	9.80	5.90	5.77	1.4840
Octyl	$C_{15}H_{25}NO_2$	104–107	0.04	71.67	71.85	10.03	10.19	5.57	5.76	1.4830
Nonyl	$C_{16}H_{27}NO_2$	135–138	0.1	72.41	72.51	10.25	10.26	5.28	5.12	1.4802
Decyl	$C_{17}H_{29}NO_2$	136–140	0.1	73.07	73.17	10.46	10.29	5.01	5.06	1.4798

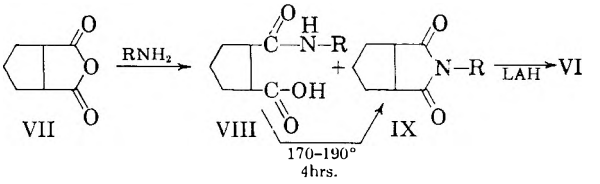
[a] All refractive indices are values obtained for the analytical samples. [b] Carbon, hydrogen, and nitrogen analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Ionic halogen analyses were performed by one of us (C. H. G.) by methods previously described, Grogan, C. H., Rice, L. M., and Reid, E. E., *J. Org. Chem.*, **20**, 50 (1955).

octane,[14] II, 3-azabicyclo[3.2.0] heptane,[15] III, various modifications including ring bridging and substitution of the isoindole, 2-azabicyclo[4.3.0]-nonane nucleus,[12] IV.



We recently reported the synthesis and properties[16] of unsymmetrical bis-ammonium salts employing the 3-azabicyclo[3.3.1]nonane nucleus, V. These compounds were either inactive or possessed a low degree of activity. This was quite surprising since activity was encountered in all modifications of the azabicyclo[4.3.0]nonanes that we investigated. Since this change amounted to changing the position of attachment on the cyclohexane ring from 1,2 to 1,3 (azabicyclo[4.3.0]-nonane to azabicyclo[3.3.1]nonane), we were prompted to investigate the effects of changing the attachment on the cyclopentane ring from 1,3 to 1,2 (azabicyclo[3.2.1]octane to azabicyclo-[3.3.0]octane). This led to the synthesis and screening of *N*-substituted derivatives of this nucleus, VI, which are reported herein.

As in past series reported, the desired *N*-dialkylaminoalkyl bases were most readily accessible by a two step process from the appropriate anhydride. In the present series of compounds the key anhydride was *cis*-1,2-cyclopentane dicarboxylic anhydride. This anhydride was prepared according to the procedure of Fuson and Cole.[17]



The anhydride, VII, was allowed to react with either primary alkyl amines, dialkylaminoalkylamines, or heterocyclicalkylamines to yield a mixture of the amic acid, VIII, and imide, IX. This mixture was then heated at 170–190° for several hours to convert all amic acid to the imide. Products from all three types of amines were isolated by distillation *in vacuo* in an excellent state of purity and in yields of from 70–90% on runs of 10–25 grams.

Table I lists several *N*-alkyl imides thus prepared together with pertinent physical data. Table III lists some *N*-dialkylaminoalkyl imides similarly prepared, their hydrochlorides and methiodides, with pertinent physical data. All of the imides in each series were stable colorless oily liquids.

Reduction of the imides to the corresponding bicyclic bases, VI, was accomplished in all cases by adding the imide dissolved in anhydrous ether to an ethereal solution of lithium aluminum hydride. The reaction was clean and proceeded in the expected manner to give the desired bases in an excellent state of purity and in yields ranging from 70–90% on runs of 10–25 grams. These tertiary amine heterocycles were all stable colorless liquids with typical amine properties. Representative *N*-alkyl-substituted 3-azabicyclo[3.3.0]octanes were reduced and are listed in Table II together with their hydrochlorides, methiodides, and pic-

(14) L. M. Rice and C. H. Grogan, *J. Org. Chem.*, **22**, 185 (1957).

(15) L. M. Rice and C. H. Grogan, *J. Org. Chem.*, **22**, 1100 (1957).

(16) L. M. Rice and C. H. Grogan, *J. Org. Chem.*, **23**, 844 (1958).

(17) R. C. Fuson and W. Cole, *J. Am. Chem. Soc.*, **60**, 1237 (1938).

TABLE II

N-ALKYL-3-AZABICYCLO[3.3.0]OCTANES

Alkyl	Formula	B.P., °C.	Mm.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	n_D^{25}
Methyl	$C_8H_{15}N$	69–70	48.0	76.74	76.88	12.07	11.94	11.19	11.48	1.4648
Butyl	$C_{11}H_{21}N$	120–123	52.0	78.97	79.02	12.65	12.52	8.37	8.56	1.4655
Hexyl	$C_{13}H_{25}N$	108–112	10.0	79.93	79.56	12.90	12.77	7.17	7.40	1.4665
Decyl	$C_{17}H_{33}N$	87–94	0.1	81.20	81.26	13.23	13.18	5.57	5.74	1.4670

Derivatives of Above Bases

Hydrochloride[a] Formula	M.P., °C.	Chlorine, % Calcd.	Chlorine, % Found	Methiodide[a] Formula	M.P., °C.	Iodine, % Calcd.	Iodine, % Found	Picrate[a] Formula	M.P., °C.	Nitrogen, % Calcd.	Nitrogen, % Found
$C_8H_{16}ClN$	150–151	21.93	21.91	$C_9H_{18}IN$	205–206	47.51	47.69	$C_{14}H_{18}N_4O_7$	226–227	15.81	15.59
$C_{11}H_{22}ClN$	237–239	17.40	17.33	$C_{12}H_{24}IN$	150–151	41.04	41.38	$C_{17}H_{24}N_4O_7$	175–176	14.14	14.12
$C_{13}H_{26}ClN$	210–211	15.30	15.19	$C_{14}H_{28}IN$	123–125	37.63	37.25	$C_{19}H_{28}N_4O_7$	135–136	13.20	13.44
$C_{17}H_{34}ClN$	192–194	12.31	12.60	$C_{18}H_{36}IN$	177–179	32.26	32.51	.....	.....	...	...

[a] All hydrochlorides, methiodides, dihydrochlorides, and bis-methiodides were recrystallized from isopropyl alcohol–ether mixtures; picrates were recrystallized from water-ethanol. Usually one or two recrystallizations yielded constant melting derivatives. All melting and boiling points are uncorrected.

TABLE III

N-DIALKYLAMINOALKYL-3-AZABICYCLO[3.3.0]OCTANE-2,4-DIONES

	Substituent	Formula	B.P., °C.	MM.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	n_D^{20}
1	Dimethylaminoethyl	$C_{11}H_{18}N_2O_2$	93–98	0.3	62.83	63.07	8.63	8.85	13.32	13.40	1.4958
2	Dimethylaminopropyl	$C_{12}H_{20}N_2O_2$	87–90	0.1	64.25	64.48	8.99	9.13	12.49	12.22	1.4940
3	Diethylaminoethyl	$C_{13}H_{22}N_2O_2$	105–115	0.3	65.51	65.56	9.31	9.55	11.76	11.51	1.4930
4	Diethylaminopropyl	$C_{14}H_{24}N_2O_2$	108–113	0.08	66.63	66.87	9.59	9.45	11.10	11.47	1.4908
5	Morpholinopropyl	$C_{14}H_{22}N_2O_3$	145–155	0.08	63.13	63.63	8.33	8.16	10.52	10.47	1.5115

Derivatives of Above Bases

	Hydrochloride Formula	M.P., °C	Chlorine, % Calcd.	Chlorine, % Found	Methiodide Formula	M.P., °C.	Iodine, % Calcd.	Iodine, % Found
1	$C_{11}H_{19}ClN_2O_2$	199–200	14.37	14.35	$C_{12}H_{21}IN_2O_2$	180–181	36.03	36.07
2	$C_{12}H_{21}ClN_2O_2$	173–174	13.60	13.70	$C_{13}H_{23}IN_2O_2$	230–231	34.65	34.61
3	$C_{13}H_{23}ClN_2O_2$	183–185	12.90	13.23	$C_{14}H_{25}IN_2O_2$	.....	...	...
4	$C_{14}H_{25}ClN_2O_2$	123–124	12.28	12.56	$C_{15}H_{27}IN_2O_2$	114–115	32.18	32.02
5	$C_{14}H_{23}ClN_2O_3$	184–185	11.71	11.66	$C_{15}H_{25}IN_2O_3$	201–202	31.08	30.97

rates. Representative *N*-dialkylaminoalkyl substituted 3-azabicyclo[3.3.0]octanes thus prepared are listed in Table IV together with their dihydrochloride and bis-methonium salts.

Members from each series were screened for hypotensive activity in dogs by techniques previously described.[18] As expected from previous series, the methiodides of the *N*-alkyl bases, hydrochlorides and methiodides of the *N*-dialkylaminoalkylimides, and hydrochlorides of the bicyclic bases were inactive. However, conversion of the *N*-dialkylaminoalkyl bicyclic bases to bis-quaternary methonium salts resulted in compounds with good activity. Hence it has been shown that in the cyclopentane-derived bicyclic structure a change in position of attachment of the second ring bearing the nitrogen atom from 1,3, I, II, to 1,2, VI, did not result in loss of activity. In the cyclohexane derived structures, on the other hand, a change in bridging from 1,2 (IV) to 1,3 (V) resulted in almost complete loss of activity.

In summary of our extensive work on the type of compound illustrated by formula A, we should like to emphasize that even though broad general hypotensive activity was encountered in both symmetrical and unsymmetrical permutations of this structure, subtle differences in toxicity, potency, duration of effect, therapeutic ratio, and therapeutic effectiveness were noted. For example some of the compounds from II and IV, although in both cases nearly equally potent by injection, have a ratio of activity on oral administration of about 2 to 1. That II is more effective orally, although similar in over-all structural characteristics, has

(18) W. E. O'Malley, G. Winkler, L. M. Rice, and C. F. Geschickter, *J. Am. Pharm. Assoc. Sci Ed.*, **46**, 346 (1957).

TABLE IV

N-DIALKYLAMINOALKYL-3-AZABICYCLO[3.3.0]OCTANES

	Substituent	Formula	B.P., °C.	MM.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	n_D^{25}
1	Dimethylaminoethyl	$C_{11}H_{22}N_2$	93–95	10.0	72.47	72.41	12.16	12.32	15.37	15.43	1.4755
2	Dimethylaminopropyl	$C_{12}H_{24}N_2$	102–104	5.0	73.41	73.70	12.32	12.28	14.27	14.46	1.4742
3	Diethylaminoethyl	$C_{13}N_{26}N_2$	59–63	0.08	74.22	74.55	12.46	12.16	13.32	13.54	1.4757
4	Diethylaminopropyl	$C_{14}H_{28}N_2$	99–103	1.2	74.94	74.92	12.58	12.48	12.49	12.54	1.4746
5	Morpholinopropyl	$C_{14}H_{26}N_2O$	94–98	0.1	70.54	70.74	10.99	11.01	11.75	11.99	1.4957

Derivatives of Above Bases

	Dihydrochloride Formula	M.P., °C.	Chlorine, % Calcd.	Chlorine, % Found	Dimethiodide Formula	M.P., °C.	Iodine, % Calcd.	Iodine, % Found
1	$C_{11}H_{24}Cl_2N_2$	296–298	27.78	27.78	$C_{13}H_{28}I_2N_2$	236–238	54.45	54.28
2	$C_{12}H_{26}Cl_2N_2$	261–262	26.33	26.20	$C_{14}H_{30}I_2N_2$	256–257	52.85	52.97
3	$C_{13}H_{28}Cl_2N_2$	210–211	25.03	24.83	$C_{15}H_{32}I_2N_2$	213–214	51.35	51.11
4	$C_{14}H_{30}Cl_2N_2$	204–205	23.85	23.53	$C_{16}H_{34}I_2N_2$	209–210	49.94	49.88
5	$C_{14}H_{28}Cl_2N_2O$	265–267	22.78	22.59	$C_{16}H_{32}I_2N_2O$	234–236	48.60	48.48

been demonstrated clinically. The bis-methionium derivative of the *N*-dimethylaminopropyl base derived from II has been under clinical trials by Wyeth Laboratories (Wy-1395)[19] for over a year and is believed to possess centrally acting components in addition to its ganglioplegic properties.

Of all the compounds prepared in the various series, the compounds derived from IV with an additional oxygen bridge in the cyclohexane ring and bearing methyl substituents on this ring were the finest examples of almost ideal agents.[20] The bis-methonium salts of the compound, *N*-dimethylaminoethyl - 4 - methyl - 4,7 - endoxyperhydroisoindole (Wy-1263)[18,21] possessed an extremely low toxicity in rats, dogs, and humans. Yet it was a very potent hypotensive agent of long duration of action in parenterally administered doses of a fraction of a mg./kg. In addition it had a therapeutic plateau effect which makes it the safest drug we have ever seen for lowering blood pressure. This is particularly important from a safety point of view when such agents are used to titrate patients with severe or malignant hypertension. In addition to this use in more critical cases, it can be employed orally and can satisfactorily control mild and severe types of hypertension.

EXPERIMENTAL

The general synthesizing procedures employed in the present series of compounds are illustrated by the following examples.

3-Methyl-3-azabicyclo[3.3.0]octane-2,4-dione. cis-1,2-Cyclopentane dicarboxylic anhydride, 49 g. (0.35 mole) was placed in a 200-ml. round bottom flask and 96 g. (0.386 mole) of a 12.5% aqueous solution of methylamine was added. The mixture was stirred vigorously during the addition of the amine and cooled as needed to prevent loss of amine. When the initial reaction had subsided, the solution was heated to boiling. After all water had been boiled off, the temperature was slowly raised to 220°. The crude product was allowed to cool and then distilled *in vacuo* to yield 43 g., 80%, of product with b.p. 144–148°/29 mm., n_D^{20} 1.5026.

3-Azabicyclo[3.3.0]octane-2,4-dione. The simple imide of *cis*-1,2-cyclopentane dicarboxylic anhydride was readily formed in a manner analogous to that employed to synthesize the *N*-methyl imide when concentrated aqueous ammonia was used instead of methyl amine. The crude product was recrystallized from water and melted at 85–87°.

Anal. Calcd. for $C_7H_9NO_2$: C, 60.41; H, 6.52; N, 10.07. Found: C, 60.60; H, 6.56; N, 10.07.

3-Methyl-3-azabicyclo[3.3.0]octane. A solution of 15 g. (excess) of lithium aluminum hydride was dissolved in 800 ml. of anhydrous ether in a 2-liter, 3-necked, reaction flask equipped with Hershberg stirrer, dropping funnel, reflux condenser, and drying tube. A solution of 36 g. (0.235 mole) of 3-methyl-3-azabicyclo [3.3.0]octane-2,4-dione in 400 ml. of anhydrous ether was added dropwise with stirring at such a rate as to just maintain reflux of the ether. When addition was complete, the mixture was stirred for 2 hr. and then decomposed by the dropwise addition of water. This was added so as to just maintain reflux of the ether; and then a 5-ml. excess was added. The inorganic solid precipitate was filtered off with rapid suction, pressed tightly, and washed three times with 100-ml. portions of ether. The filtrate and washings were combined and dried over anhydrous sodium sulfate. The ether was stripped off and the residue distilled under reduced pressure to yield the base, 21 g. 71%, b.p. 69–70°/48 mm., n_D^{20} 1.4648.

The *hydrochloride* was prepared in isopropyl alcohol with excess alcoholic HCl and precipitated with ether. On recrystallization from isopropyl alcohol–ether, it melted at 150–151°.

The *methiodide* was prepared in isopropyl alcohol with a slight excess of methyl iodide at room temperature and recrystallized from isopropyl alcohol–ether, m.p. 205–206°.

The *picrate* was prepared in the usual way, m.p. 226–227°.

3-Dimethylaminopropyl-3-azabicyclo[3.3.0]octane-2,4-dione was prepared by causing to react 8 g. (0.078) mole of dimethylaminopropylamine with 10.0 g. (0.071 mole) of *cis*-1,2-cyclopentane dicarboxylic anhydride and heating the resulting homogeneous reaction mixture at 170–190° for

(19) W. E. O'Malley, G. W. Haemmerli, L. M. Rice, and C. F. Geschickter, *J. Am. Pharm. Assoc. Sci. Ed.*, **47**, 263 (1958).

(20) C. H. Grogan and L. M. Rice, U. S. Patent **2,784,199**, March 5, 1957.

(21) G. Winkler, W. E. O'Malley, L. M. Rice, and C. F. Geschickter, *J. Am. Pharm. Assoc. Sci. Ed.*, **47**, 620 (1958).

2 hr. The imide was isolated by distillation *in vacuo* to yield 12.4 g., 78%, of product, b.p. 87–90°/0.1 mm., n_D^{20} 1.4940. The *hydrochloride* was prepared as described, m.p. 173–174°. The *methiodide* was prepared as described, m.p. 230–231°.

3-Dimethylaminopropyl-3-azabicyclo[3.3.0]octane. The *N*-dimethylaminopropyl base was obtained in a manner analogous to that of the simple *N*-methyl base on reduction of the *N*-dimethylaminopropyl imide with lithium aluminum hydride in anhydrous ether. From 18 g. (0.080 mole) of the imide there was obtained 14 g., 89% of the base with b.p. 102–104°/5 mm., n_D^{20} 1.4742. The *dihydrochloride* was prepared in alcohol in the usual way and on recrystallization melted at 261–262°. The *bis-methiodide* was prepared by refluxing the base with a 10% excess of methyl iodide in methanol for 1 hr. The bis-methonium salt was collected on cooling and recrystallized from methanol-ether, m.p. 256–257°.

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[CONTRIBUTION FROM THE PHYSIOLOGY DEPARTMENT, TUFTS UNIVERSITY SCHOOL OF MEDICINE]

Chemistry of Pyrimidines. I. The Reaction of Bromine with Uracils[1-3]

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Uracils react with bromine in aqueous solution to form 5-bromo-6-hydroxyhydro derivatives. Upon dehydration in solution the latter form 5-bromo derivatives, which in turn with excess bromine, form 5,5-dibromo-6-hydroxyhydro derivatives. The mechanism of the formation of the 5-bromo derivatives from the latter has been elucidated.

In our study of the effects of ultraviolet irradiation on nucleic acids, we have used a number of pyrimidine derivatives as model compounds. Several common reactions have been studied and certain inconsistencies in the literature have been noted. It was the purpose of the present work to clarify these inconsistencies.

In 1907, Wheeler and Johnson[4] first observed the colored reaction product obtained by the action of bromine on uracil and cytosine and since then this reaction has become a well known color test for uracils and cytosines. More recently, a colorimetric method for the determination of uracil and cytosine[5] has been based upon this bromine reaction. The reaction also played an important part in the structural determination of pyrimidine nucleosides and the preparation of derivatives.[6] In 1940. Johnson *et al.* concluded that "5,5-dibromo-4(6)-hydroxyhydrouracil (IVA) decomposed spontaneously and quantitatively to 5-bromouracil and HOBr."[7] In order to prove their statement that HOBr was formed and subsequently served as an oxidizing agent, Johnson *et al.* allowed the dibromo compound to react with thiourea, ethylenethiourea, malonic acid, and barbituric acid and ketene.[7,8] Some interesting observations on the reaction of bromine with pyrimidine compounds have also been reported by Cohn.[9] In the present report we wish to propose a possible mechanism for this bromine reaction.

RESULTS AND DISCUSSION

The addition of one mole equivalent of bromine to uracil (IA) or 1,3-dimethyluracil (IB) in aqueous solution resulted in the formation of 5-bromo-6-hydroxyhydro derivatives (IIA or IIB). The existence of (IIA) or (IIB) was indicated by the loss of the ultraviolet spectrum of IA or IB, the isolation of 6-hydroxyhydro-1,3-dimethyluracil[10] by hydrogenolysis and the formation of 5-bromo-derivatives (IIIA or IIIB). The dehydration of IIA or IIB to form IIIA or IIIB proceeded spontaneously and quantitatively and thus provided an excellent method for the preparation of III. Therefore, it seemed that Johnson's statements[7] to the effect that IVA decomposed spontaneously and quantitatively to III could actually hold for II. A thorough study of IV was made in order to clarify these different views. IV was prepared by the addition of one mole equivalent of bromine to 5-bromo- derivatives (III) in aqueous solution. However, the bromine analysis of the product obtained after repeated crystallization from hot water were low (IVA, found: 54.05, 54.38; IVB, found: 49.15)

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(2) The author wishes to thank M. Apicella, L. A. Johnson, and R. Weintraub for their able assistance.

(3) A preliminary report has been published in *Nature*, **180**, 91 (1957).

(4) H. L. Wheeler and T. B. Johnson, *J. Biol. Chem.*, **3**, *Am. Chem. J.*, **42**, 30 (1909); H. L. Wheeler and L. M. Liddle, *J. Am. Chem. Soc.*, **30**, 1152 (1908).

(5) M. Soodak, A. Pircio, and L. R. Cerecedo, *J. Biol. Chem.*, **181**, 712 (1949).

(6) P. A. Levene, *J. Biol. Chem.*, **63**, 653 (1925); "Nucleic Acids", ACS Monograph No. 56, pp. 54 and pp. 148 (Chemical Catalog Co., Inc., New York, 1931).

(7) T. B. Johnson, *J. Am. Chem. Soc.*, **62**, 2269 (1940); also G. E. Hilbert and E. F. Jansen, *J. Am. Chem. Soc.*, **56**, 136 (1934).

(8) T. B. Johnson and C. O. Edens, *J. Am. Chem. Soc.*, **63**, 1058 (1941); T. B. Johnson and M. J. Winton, *J. Am. Chem. Soc.*, **63**, 2379 (1941); M. Fytelson and T. B. Johnson, *J. Am. Chem. Soc.*, **64**, 306 (1942).

(9) W. E. Cohn, *Biochem. J.*, **64**, 28P (1956).

(10) S. Y. Wang, M. A. Apicella, and B. R. Stone, *J. Am. Chem. Soc.*, **78**, 4180 (1956).

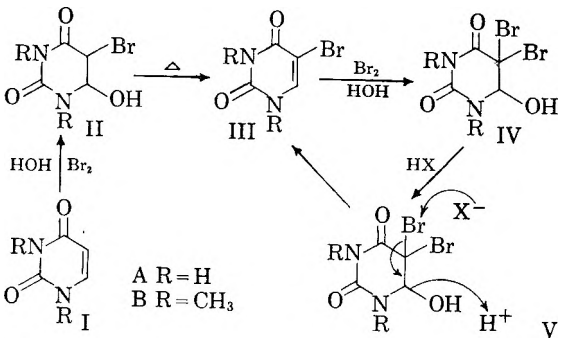
for both compounds. These results led us to recrystallize the compounds from nonaqueous solution because the above bromine analysis checked very well with $^1/_2H_2O$ of crystallization (IVA, calcd. 54.02; IVB, calcd. 49.18). Both compounds dissolved easily in acetone and were crystallized out by the addition of petroleum ether (30–60°) and the bromine analyses were found to be correct. After drying, the compounds which were crystallized from organic solvents could be kept for a long period of time without decomposition. Therefore, this suggested that the instability of IV is probably due to the presence of water of crystallization. (Levene and Johnson did not observe this.)

As for the mechanism of the formation of 5-bromo-derivatives (III) from the dibromo derivatives (IV), the following experiments were carried out. IVA and IVB in 2×10^{-2} *M* aqueous solution were heated to reflux for 8 hr. or more. A solution of IVA gave a maximum at 275 mμ (ϵ 3.9×10^3) and a solution of IVB gave a maximum at 280 mμ (ϵ 3.4×10^3), thus indicating about 50% conversion to IIIA and IIIB, which was confirmed by the isolation and identification of IIIA and IIIB from the above experiments. This suggested that hydrogen bromide, resulting from the hydrolysis of dibromo derivatives (IV), catalyzed the formation of III. When IVA and IVB in 1×10^{-4} *M* aqueous solution were heated under reflux for 24 hr. or more, no increase in ultraviolet absorption was observed at any time. This is probably due to the hydrolysis of IV to form isodialuric acid. However, when the reaction was carried out in 2 *N* HCl or HBr, the absorption at 275 mμ for IIIa ($\lambda_{max}^{2N\ HCl}$ 276 mμ, ϵ 7.2 $\times 10^3$) and at 280 mμ for IIIB ($\lambda_{max}^{2N\ HCl}$ 283 mμ, ϵ 7.8 $\times 10^3$) gradually increased to more than 80% of that for IIIA and IIIB at the end of 8 hr. The above observations indicate that III is formed from IV only when HX is present. The probable reason for Levene's[6] statement that "the dibromo compound is undoubtedly the original product which formed immediately on addition of bromine" is that he overlooked the existence of II, which he did not observe because of the inability to isolate these derivatives.

Most workers have been under the impression that IV is highly unstable (which belief now appears untenable), since they used the method of Levene[11] for the preparation. This method requires the addition of bromine until the color of the solution remains permanently yellow. However, we observed that if the reaction was carried out at or below room temperature, the yellow color appeared after one mole equivalent of bromine had been added to the solution. Thus, the isolation of IV is not possible under these conditions. The formation of dibromo compounds (IV) or the disappearance of the yellow color for the second mole equivalent of bromine is dependent on the rate of the formation of III and thus is determined by the rate of dehydration of II. The rate of dehydration seems to be influenced by the bulkiness of neighboring groups (N_1) to the 6-hydroxy group. For example, at room temperature and *p*H 2, IIA is dehydrated in less than 10 min., IIB is completed in 2 hr., but for uridine no more than 10% dehydration was observed in 24 hr. However, when heated on a steam bath for 10 min., these three compounds were all completely dehydrated.

From the above results, it appears that uracil derivatives, whether substituted at position 3 or not, show the same chemical behavior in reactions with bromine. There may be differences between them but they are only quantitative instead of qualitative.

In conclusion, we suggest that IV is formed from III, and III in turn is formed from II. The formation of III from IV is catalyzed by HX and may proceed *via* the transition state V.



EXPERIMENTAL[12]

5-Bromouracil (IIIA). Uracil (2×10^{-2} mole) was pulverized and suspended in 40 cc. of water. One mole equivalent of bromine (1.04 ml.) was added with swirling and a clear solution resulted. The reaction solution was then heated on a steam bath for 25 min. and a crystalline product started to appear after 10 min. of heating. After cooling, the product was collected and washed carefully with warm water. Over 90% yield of the compound was collected. It did not melt up to 300° but decomposed and sublimed.[4,6]

$\lambda_{max}^{H_2O}$ 276 mμ, ϵ 7.30×10^3; $\lambda_{min}^{H_2O}$ 241 mμ, ϵ 1.76×10^3; λ280/λ260 1.47, λ250/λ260 0.52; (*p*H 5.6)

Anal. Calcd. for $C_4H_3O_2N_2Br$: N, 14.67; Br, 41.84; Found: N, 14.81; Br, 41.51.

5-Bromo-1,3-dimethyluracil (IIIB). 1,3-Dimethyluracil (2×10^{-2} mole) was dissolved in 20 cc. of water and the above procedure for making IIIA was followed exactly. A yield of over 90% of IIIB, m.p. 184–185°, was obtained. Mixed melting point with an authentic sample 184–185°; $\lambda_{max}^{H_2O}$ 283 mμ, ϵ 8.57×10^3; $\lambda_{min}^{H_2O}$ 246 mμ, ϵ 1.57×10^3 [10,13]; λ280/λ260 0.24, λ250/λ260 0.49.

5,5-dibromo-6-hydroxyhydrocil (IVA). Pulverized 5-bromouracil (2×10^{-2}*M*) was suspended in 40 cc. of water and 1.04 ml. of bromine was added. The reaction mixture,

(11) P. A. Levene, *J. Biol. Chem.*, **63**, 683 (1925).

(12) All melting points are uncorrected and were taken with a Fisher-Johns melting point apparatus. The analyses were carried out by Dr. S. M. Nagy and his associates, Microchemical Laboratory, Massachusetts Institute of Technology. Ultraviolet spectra were determined with Beckman spectrophotometer, model DU.

(13) T. B. Johnson and S. H. Clapp, *J. Biol. Chem.*, **5**, 62 (1909).

in a stoppered flask, was stirred for about 6 hr. At the end white powder-like crystals were collected and washed with chilled water. Over 80% of the theoretical amount was obtained and an additional 10% more was obtained after the mother liquor had been concentrated to about one third of its original volume with a stream of nitrogen. This compound melted at 209–211° with strong effervescence, then resolidified.[4]

Anal. Calcd. for $C_4H_4N_2Br_2O_3 \cdot {}^1/_2H_2O$: C, 16.18; H, 1.70; N, 9.44; Br, 53.82. Found: C, 16.09; H, 1.64; Br, 54.05.

This compound was recrystallized from acetone–petroleum ether (30–60°), m.p. 210° with strong effervescence, then resolidified.

Anal. Calcd. for $C_4H_4O_3N_2Br_2$: Br, 55.51; Found: Br, 55.12.

5,5-Dibromo-6-hydroxy-1,3-dimethylhydrouracil (IVB). Pulverized 5-bromo-1,3-dimethyluracil (IIIB) was treated identically as the above procedure and gave over 80% of the theoretical yield. Crystallization from hot water yielded a product with a m.p. 136–137°.[12]

Anal. Calcd. for $C_6H_8O_3N_2Br_2 \cdot {}^1/_2H_2O$: Br, 49.18. Found: Br, 49.15.

Crystallization from acetone-petroleum ether (30–60°) instead of water, yielded a product with a m.p. 139–140°.

Anal. Calcd. for $C_6H_8O_3N_2Br_2$: Br, 50.58. Found: Br, 50.50

Effect of reflux on 5,5-dibromo-6-hydroxyhydrouracil (IVA) in 2 × 10⁻²M aqueous solution. A $2 \times 10^{-2}M$ solution of IVA (0.2879 g. in 50 cc.) was heated under reflux. At one hour intervals, a 0.5 ml. sample of the solution was withdrawn and diluted to 100 ml. in a volumetric flask. The ultraviolet spectrum of each sample was determined. Prior to reflux the solution had an initial *p*H of 5.88 and after, a *p*H of 3.90. The readings were obtained as shown in Table I.

TABLE I

Time, Hr.	2×10^{-2} *M* in H_2O		1×10^{-4} *M* in 2*N* HCl	
	IVA, ϵ_{275}, $\times 10^{-3}$	IVB, ϵ_{280}, $\times 10^{-3}$	IVA, ϵ_{275}, $\times 10^{-3}$	IVB, ϵ_{280}, $\times 10^{-3}$
0	0.23	0.37	0.22	0.39
1	0.77	0.92	3.19	3.95
2	1.75	1.67	3.90	5.60
3	2.66	2.01	4.48	6.01
4	3.39	2.97	4.98	6.20
5	3.89	3.39	5.21	6.30
6	4.00	3.62	5.49	6.21
7	3.76	3.65	5.45	6.21
8	3.80	3.77	5.59	6.21

Effect of reflux on 5,5-dibromo-6-hydroxy-1,3-dimethylhydrouracil (IVB) *in 2 × 10⁻²M aqueous solution.* A $2 \times 10^{-2}M$ solution of IVB (0.3159 g. in 50 cc.) was treated in a similar manner as above. The readings are shown in the table.

Isolation of 5-bromouracil (IIIA) *from aqeuous solution of 2 × 10⁻²M of* IVA *by reflux.* A solution containing 0.576 g. of IVA dissolved in 100 cc. H_2O ($2 \times 10^{-2}M$) was heated under reflux for 8 hr. The final *p*H reading was 1.8 and extinction at $\lambda_{275}^{H_2O}$ was ϵ 3.7×10^3. The solution was evaporated to dryness and gave a crude yield of 0.3143 g. After two recrystallizations from absolute methanol, a crystalline product which decomposed and sublimed without melting up to 300° was obtained. Its ultraviolet spectrum was identical with the standard curve of IIIA and the optical density ratios were λ280/λ260, 1.49 and λ260/λ240, 2.66 as compared to the standard values of 1.47 and 2.61, respectively.

Isolation of 5-bromo-1,3-dimethyluracil (IIIB) *from aqueous solution of 2 × 10⁻²M of* IVB *by reflux.* A solution containing 0.316 g. of IVB dissolved in 50 cc. of H_2O ($2 \times 10^{-2}M$) was heated under reflux for 8 hr. The final reading of extinction at $\lambda_{280}^{H_2O}$ was ϵ 3.6×10^3. The solution was extracted six times with 25 cc. portions of chloroform and the organic layers were filtered through anhydrous sodium sulfate. The crude crystalline residue, after evaporation of chloroform, weighed 89 mg. One recrystallization from absolute ethanol gave a product with a m.p. 184–185° and mixed m.p. 184–185° (with authentic 5-bromo-1,3-dimethyluracil). Also identical ultraviolet spectra for both were obtained.

Effect of reflux on 1 × 10⁻⁴M aqueous solution of 5,5-dibromo-6-hydroxyhydrouracil (IVA). A solution of $1 \times 10^{-4}M$ of the compound IVA in water was heated under reflux. The ultraviolet spectrum of each sample which had been pipetted from the solution at certain time intervals was determined from 220–300 mμ. The readings at 275 mμ were as follows:

Time, hr.	0	3	6	12	24
$\epsilon_{275} \times 10^{-3}$	0.18	0.38	0.41	0.38	0.33

Effect of reflux on 1 × 10⁻⁴M aqueous solution of 5,5-dibromo-6-hydroxy-1,3-dimethylhydrouracil (IVB). A solution of $1 \times 10^{-4}M$ of the compound (IVB) in water was treated in a similar manner as above. The readings at 280 mμ were as follows:

Time, hr.	0	3	6	12	24
$\epsilon_{280} \times 10^{-3}$	0.27	0.14	0.18	0.11	0.21

Effect of reflux in acid (2N HCl or HBr) on 1 × 10⁻⁴M solution of 5,5-dibromo-6-hydroxyhydrouracil (IVA). A solution of $1 \times 10^{-4}M$ of the compound (IVA) in 2*N* HCl was heated under reflux, in a flask. The ultraviolet spectrum of each sample at certain time intervals was determined from 220–300 mμ. The readings at 275 mμ are shown in the table.

Effect of reflux in acid (2N HCl or HBr) on 1 × 10⁻⁴M solution of 5,5-dibromo-6-hydroxy-1,3-dimethylhydrouracil (IVB). A solution of $1 \times 10^{-4}M$ of the compound (IVB) in 2*N* HCl was heated under reflux, and the readings were taken in exactly the same manner as above and are shown in Table I.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PENNSYLVANIA]

Synthesis of 2-Thio Analogs of Thiamine[1]

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The synthesis of "methioprim" analogs of thiamine is discussed. The pyrimidylmethyl halides used as intermediates were found to undergo solvolysis readily in warm alcoholic solvents. Physical properties and biological activity data tend to indicate previously reported preparations were frequently the alcoholysis products or mixtures of the alcoholysis product and the desired analog.

INTRODUCTION

Because of our interest in "methioprim" (2-methylthio-4-amino-5-hydroxymethylpyrimidine) (I) as an antimetabolite,[2] we have undertaken a restudy of the synthesis and biological activity of certain previously reported methioprim analogs of thiamine. This paper is concerned with the synthesis of the previously reported 4-methyl-5-(β-hydroxyethyl)-*N*-(2-ethylthio-4-amino-5-pyrimidylmethyl)thiazolium bromide (II)[3] and its hydrobromide (III)[4] and of 4-methyl-5-(β-hydroxyethyl)-*N*-(2-methylthio-4-amino-5-pyrimidylmethyl)thiazolium chloride hydrochloride (IV).[4,5]

The synthetic route to these compounds involved the condensation of the halides of the pyrimidine moiety with the thiazole moiety of thiamine in alcoholic media, in analogy with the routine methods of synthesis for thiamine.[6] We wish to report in this paper that our studies indicate that alcoholysis of the halides of these thiopyrimidines may occur and that some of the thiamine analogy prepared earlier were in fact alcoholysis products.

DISCUSSION

We have found that 2-methylthio-4-amino-5-bromomethylpyrimidine hydrobromide (V) readily undergoes alcoholysis in hot isopropyl alcohol to give 2-methylthio-4-amino-5-isopropoxymethylpyrimidine hydrobromide (VI), analogously to previous observations in methanol and ethanol.[2a] This alcoholysis occurs even when the solution contains an equivalent amount of the thiazole moiety of thiamine. Alcoholysis is also observed with 2-ethylthio-4-amino-5-bromomethylpyrimidine hydrobromide (VII) and 2-methylthio-4-amino-5-chloromethylpyrimidine hydrochloride (VIII), 2-ethylthio-4-amino-5-isopropoxymethylpyrimidine hydrobromide (IX) and 2-methylthio-4-amino-5-isopropoxymethylpyrimidine hydrochloride (X) being obtained as the products.

In order to avoid alcoholysis of the halide intermediates, we have carried out the synthesis of these thio analogs using nonhydroxylic solvents, and the products are indeed found to differ from the compounds obtained using alcoholic solvents.

It is to be noted that with some compounds in this series, the differences in the elementary composition are not large enough to differentiate effectively between the desired thiamine analogs and the corresponding alcoholysis products. Thus, the differences in the calculated percentage analysis for carbon, hydrogen, and nitrogen for the free base of 2-ethylthiothiamine (II) and the isopropoxy compound from alcoholysis (IX) are surprisingly small (Table I). Since analyses for only these three elements were reported by Dornow and Petsch, their analyses are not sufficient to identify their product conclusively. Unlike other thiamine analogs prepared by the same methods, which are obtained as salts, II was reported by Dornow and Petsch to correspond to the free base having only

TABLE I

CALCULATED PERCENTAGE COMPOSITION

Compound	C	H	Br	N	S
2-Ethylthiothiamine, as HBr salt $C_{13}H_{20}Br_3N_4OS$	33.06	4.27	33.84	11.86	13.58
2-Ethylthiothiamine, as free base $C_{13}H_{19}BrN_4OS$	39.89	4.89	20.42	14.32	16.39
2-Ethylthio-4-amino-5-isopropoxymethylpyrimidine $C_{10}H_{18}BrN_3OS$	38.96	5.88	25.92	13.63	10.40

(1) Supported in part by U. S. Public Health Service Grant Cy-2714.

(2) (a) T. L. V. Ulbricht and C. C. Price, *J. Org. Chem.*, 21, 567 (1956); *Chem. & Ind. (London)*, 1221 (1955); T. Okuda and C. C. Price, *J. Org. Chem.*, 22, 1719 (1957); T. Okuda and C. C. Price, *J. Org. Chem.*, in press. (b) D. B. McNair-Scott, T. L. V. Ulbricht, M. L. Rogers, E. Chu, and C. Rose, *Cancer Research*, in press; D. F. Dunning, T. L. V. Ulbricht, C. C. Price, and R. Jones, Jr., unpublished results; R. Guthrie, M. E. Loebeck, and M. J. Hillman, *Proc. Soc. Exptl. Biol. Med.*, 94, 792 (1957); R. Guthrie *et al.*, *Proc. Am. Assoc. Cancer Research*, 2, 113 (1956); I. J. Slotnick *et al.*, *Proc. Am. Assoc. Cancer Research*, 3, 251 (1957); F. Rosen, J. F. Holland, and C. A. Nichol, *Proc. Am. Assoc. Cancer Research*, 3, 243 (1957).

(3) A. Dornow and G. Petsch, *Ann.*, 588, 45 (1954).

(4) T. Sakuragi, *Arch. Biochem. Biophys.*, 74, 362 (1958).

(5) T. L. V. Ulbricht and J. S. Gots, *Nature*, 178, 913 (1956).

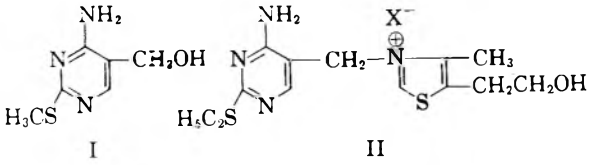
(6) R. R. Williams and J. K. Cline, *J. Am. Chem. Soc.*, 58, 1504 (1936); H. Andersag and K. Wesphal, *Ber.*, 70B, 2035 (1937).

one halogen atom, in accordance with their analysis. An additional analysis for bromide and for sulfur would enable one to differentiate between the free base and the alcoholysis product.

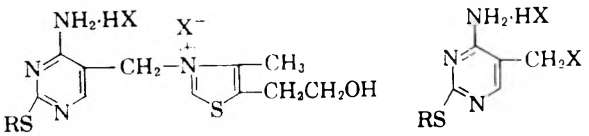
However, the melting point of our alcoholysis product (IX), 171–173° (dec.), is practically the same as that which Dornow and Petsch report for their "2-ethylthiothiamine" (172–174°, dec. at 175°), in contrast to the melting point of our 2-ethylthiothiamine hydrobromide prepared in nonalcoholic solvent (228–230°, dec.).

While this report was being prepared, a paper by T. Sakuragi[4] on an extensive series of 2-alkylthio analogs of thiamine appeared. Sakuragi prepared his 2-alkythio analogs by condensation of the halide intermediates in methanol at room temperature. The melting point reported for his 2-ethylthiothiamine hydrobromide (212–213°, dec.) is lower than ours. This lower melting point is suggestive of some competing alcoholysis even in the cold. His elementary analysis for carbon, hydrogen, and sulfur agreed well with that calculated for 2-ethylthiothiamine hydrobromide.

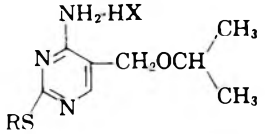
Dornow and Petsch reported their compound to have no thiamine activity when tested on Amoeba. Our alcoholysis product is also inactive. Sakuragi reports some antithiamine effectiveness for his compound. Our studies on 2-ethylthiothiamine hydrobromide are incomplete. A complete report of the biological activity of our series of methioprim analogs will be submitted for publication elsewhere by Dr. Joseph S. Gots.



I II



III. R = C_2H_5, X = Br
IV. R = CH_3, X = Cl
XI. R = CH_3, X = Br
V. R = CH_3, X = Br
VII. R = C_2H_5, X = Br
VIII. R = CH_3, X = Cl



VI. R = CH_3, X = Br
IX. R = C_2H_5, X = Br
X. R = CH_3, X = Cl

In the case of the 2-methylthiothiamine compounds, a sample sent by Ulbricht to the Roswell Park Memorial Institute as 2-methylthiothiamine hydrochloride[6a] was found to be identical to our 2-methylthio-4-amino-5-isopropoxymethylpyrimidine hydrochloride in infrared spectra and to differ from the spectra of our 2-methylthiothiamine hydrochloride prepared in nonalcoholic media. In preliminary tests with *Bacillus subtilis* our 2-methylthiothiamine hydrobromide (XI) has shown a strong inhibition of growth, whereas Ulbricht's sample has shown only a partial inhibitory action.[7]

Sakuragi also reports strong biological activity, using *Kloekera brevis* and *Lactobacillus fermenti*, for his 2-methylthiothiamine hydrobromide. His melting point is again lower than ours (202.5–204.5°, dec., as *cf.* 210–212°, dec.).[8]

EXPERIMENTAL[9]

4-Methyl-5-(β-hydroxyethyl)-N-(2-ethylthio-4-amino-5-pyrimidylmethyl)thiazolium bromide hydrobromide (III). 2-Ethylthio-4-amino-5-bromomethylpyrimidine hydrobromide[2a] (10 g., 0.0304 mole) and 5 g. (0.035 mole) of 4-methyl-5-(β-hydroxyethyl)thiazole[10] were refluxed with stirring in 100 ml. of dioxane for 3 hr. After cooling, the solvent was removed by decantation from the precipitate, and the precipitate was dissolved in 100 ml. of boiling absolute ethanol. The solution was concentrated to 50 ml. and cooled, yielding crystals which were fairly hygroscopic. The product was recrystallized from 80 ml. of absolute ethanol to give 4.3 g. of colorless crystals. Recrystallization four times more from absolute ethanol gave a product with m.p. 228–230° (dec.).

Anal. Calcd. for $C_{13}H_{20}Br_2N_4OS$: C, 33.06; H, 4.27; Br, 33.84; N, 11.86; S, 13.58. Found: C, 32.78; H, 4.43; Br, 33.53; N, 11.91; S, 13.58.

Infrared spectrum (in potassium bromide, wave length, and % absorption): 3.00 (52), 3.23 (54), 3.33 (56), 3.65 (54), 6.06 (77), 6.34 (68), 6.55 (56), 6.72 (47), 6.92 (37), 7.23 (48), 7.43 (43), 8.05 (56), 8.54 (42), 9.34 (36), 10.07 (23), 11.40 (19), 12.33 (18), 12.63 (20), 13.03 (32), 14.27 (25).

2-Ethylthio-4-amino-5-isopropoxymethylpyrimidine. 2-Ethylthio-4-amino-5-bromomethylpyrimidine hydrobromide (2 g., 0.0061 mole) was dissolved in 50 ml. of boiling isopropyl alcohol. The solution was refluxed for 30 min., and then concentrated to 4 ml. After cooling, a white, crystalline precipitate was collected and washed with a small amount of isopropyl alcohol; yield, 1.3 g., m.p. 171–173° (dec.).

Anal. Calcd. for $C_{10}H_{18}BrN_3OS$: Br, 25.92. Found: Br, 26.93, 27.09.

The crystals (1 g.) were dissolved in 10 ml. of water, and the solution was made weakly alkaline with sodium hydroxide. The white, crystalline precipitate which appeared on neutralization was collected; yield, 0.6 g. The material was recrystallized from a mixture of benzene and petroleum ether (1:5) to give colorless crystals, m.p. 72–74°.

Anal. Calcd. for $C_{10}H_{17}N_3OS$: C, 52.84; H, 7.54; N, 18.48; S, 14.10. Found: C, 53.15; H, 7.50; N, 18.71; S, 14.30.

4-Methyl-5-(β-hydroxyethyl)-N-(2-methylthio-4-amino-5-pyrimidylmethyl)thiazolium bromide hydrobromide (XI). 2-Methylthio-4-amino-5-bromomethylpyrimidine hydrobromide[2a] (20 g., 0.063 mole) and 9 g. (0.063 mole) of

(6a) This was *not* the same sample studied for biological activity at the University of Pennsylvania.[5]

(7) Private communication from M. E. Loebeck, Roswell Park Memorial Institute, to C. C. Price.

(8) In a private communication, Ulbricht reports that his compound decomposed over 160°.

(9) Melting points are uncorrected. Analyses are by Mid-west Microlab., Inc., Indianapolis, Ind.

(10) We are indebted to Dr. [illegible] for samples of this compound.

4-methyl-5-(β-hydroxyethyl)thiazole were refluxed with stirring in 100 ml. of tetrahydrofuran for 30 min. until the solid turned into a viscous mass. After cooling, the solvent was removed by decantation and the viscous material was dissolved in 100 ml. of boiling ethanol. The solution was filtered while hot and 40 ml. of acetone was added until a precipitate appeared. After cooling, a pale yellow, crystalline precipitate which was slightly hygroscopic was collected; yield, 18 g. This product was recrystallized four times from absolute ethanol to give colorless crystals which melted at 210–212° (dec.) [lit.,[4] 202.5–204.5 (dec.)].

Anal. Calcd. for $C_{12}H_{10}Br_2N_4OS$: C, 31.45; H, 3.96; Br, 34.88; N, 12.22; S, 13.99. Found: C, 31.62; H, 4.20; Br, 33.98; N, 12.67; S, 13.82.

Infrared spectrum (in potassium bromide, wave length, and % absorption): 3.03 (55); 3.30 (61), 3.67 (54), 6.05 (82), 6.35 (66), 6.56 (60), 6.73 (50), 6.92 (40), 7.22 (48), 7.43 (49), 8.05 (55), 8.51 (45), 9.34 (33), 10.25 (22), 10.60 (22), 13.02 (30).

2-Methylthio-4-amino-5-chloromethylpyrimidine hydrochloride (VIII). To a solution of 10 g. (0.06 mole) of 2-methylthio-4-amino-5-hydroxymethylpyrimidine in 600 ml. of boiling chloroform was slowly added 30 ml. (0.41 mole) of thionyl chloride, and the mixture was refluxed for 1 hr. After cooling, a white, crystalline powder was collected and washed three times with 50-ml. portions of chloroform, followed by drying at 80° for 1 hr.; yield, 13.2 g. (100%). The product did not melt below 300°. It was recrystallized from acetic acid for analysis.

Anal. Calcd. for $C_6H_9Cl_2N_3S\cdot 2H_2O$: Cl, 27.02; N, 16.03; S, 12.23. Found: Cl, 26.61; N, 15.63; S, 12.82.

4-Methyl-5-(β-hydroxyethyl)-N-(2-methylthio-4-amino-5-pyrimidylmethyl)thiazolium chloride hydrochloride (IV). (a) 2-Methylthio-4-amino-5-chloromethylpyrimidine (5 g., 0.02 mole) and 3.2 g. (0.02 mole) of 4-methyl-5-(β-hydroxyethyl)-thiazole were refluxed with stirring in 100 ml. of tetrahydrofuran for 7 hours. After cooling, a white precipitate was collected and dried at 80° for 1.5 hr.; yield, 5.2 g. The product was refluxed with 300 ml. of isopropyl alcohol and filtered. The solid (*ca.* 200 mg.) was recrystallized twice from 40 ml. of absolute ethanol, giving colorless crystals, which were dried at 110° (1 mm. Hg) for 1 hr., m.p. 218–220° (dec.).

Anal. Calcd. for $C_{12}H_{18}Cl_2N_4OS_2\cdot C_2H_6O$: C, 40.48; H, 5.82; Cl, 17.07; N, 13.49. Found: C, 40.11; H, 5.11; Cl, 16.75; N, 13.65.

The filtrate from the above product was concentrated to 30 ml., and acetone was added until a precipitate appeared. After cooling, the hygroscopic precipitate was collected; yield, 1.2 g. It did not melt below 300°.

An aqueous solution of this product, on neutralization with sodium hydroxide, gave a colorless, crystalline precipitate, which, after recrystallization from a mixture of benzene and ligroin, melted at 105–108° and showed no melting point depression on admixture with authentic 2-methylthio-4-amino-5-isopropoxymethylpyrimidine. This evidently was formed from some unreacted chloromethyl compound in the crude precipitate.

(b) 2-Methylthio-4-amino-5-chloromethylpyrimidine hydrochloride (5 g., 0.002 mole) and 3.2 g. (0.02 mole) of 4-methyl-5-(β-hydroxyethyl)thiazole were refluxed with stirring in 100 ml. of dioxane for 3 hr. After cooling, the solvent was removed by decantation and the viscous residue was dissolved in 150 ml. of hot absolute ethanol, filtered while hot, and the filtrate concentrated to 40 ml. After cooling, the crystalline precipitate was filtered and washed with absolute ethanol, and then dried at 80° overnight; yield, 2.6 g. This product was recrystallized from absolute ethanol, giving colorless crystals which melted at 199–201° (dec.).

Anal. Calcd. for $C_{12}H_{18}Cl_2N_4OS_2\cdot H_2O$: C, 37.21; H, 5.20; S, 16.55. Found: C, 37.28; H, 5.35; S, 16.16.

Infrared Spectra (T. Okuda's sample in potassium bromide, wave length, and % absorption): (a) *Alcoholate:* 3.08 (71), 3.30 (75), 3.66 (62), 6.02 (85), 6.10 (85), 6.33 (77), 6.57 (80), 6.74 (57), 6.84 (57), 7.20 (59), 7.47 (67), 8.02 (74), 8.35 (53), 8.50 (54), 9.32 (41), 10.30 (27), 10.60 (29), 11.42 (26), 12.02 (38), 12.55 (33), 13.20 (42).

(b) *Hydrate:* 3.35 (82), 3.85 (68), 6.11 (92), 6.35 (85), 6.60 (83), 6.76 (70), 7.25 (69), 7.44 (73), 8.06 (74), 8.53 (63), 9.40 (51), 10.30 (34), 10.63 (37), 11.60 (31), 12.63 (41), 13.10 (41).

2-Methylthio-4-amino-5-isopropoxymethylpyrimidine hydrochloride (X). 2-Methylthio-4-amino-5-chloromethylpyrimidine hydrochloride (2 g., 0.009 mole) was heated with 50 ml. of isopropyl alcohol, the crystals being completely dissolved in 15 min. The solution was refluxed for 15 min. more and then concentrated to 5 ml. After cooling, a colorless crystalline precipitate was collected; yield, 1.55 g. The product did not melt below 300°.

Anal. Calcd. for $C_9H_{16}ClN_3OS$: Cl, 14.19. Found: Cl, 14.18.

Infrared spectrum: (Hydrochloride, in potassium bromide, wave length, and % absorption): 3.00 (68), 3.17 (79), 3.33 (65), 3.80 (79), 6.02 (94), 6.35 (86), 6.56 (80), 7.16 (67), 7.23 (64), 7.44 (78), 7.98 (79), 8.08 (77), 8.57 (65), 8.78 (65), 8.90 (72), 9.48 (80), 10.27 (42), 10.54 (39), 10.89 (44), 11.46 (46), 11.84 (47), 12.79 (50), 13.03 (44), 13.40 (43), 14.54 (42).

Infrared spectrum of Ulbricht's sample of "2-methylthiothiamine" hydrochloride: 3.00 (64), 3.17 (72), 3.33 (60), 3.80 (72), 6.02 (91), 6.35 (79), 6.56 (73), 7.16 (62), 7.23 (61), 7.44 (71), 7.98 (71), 8.08 (70), 8.57 (60), 8.78 (60), 8.90 (67), 9.48 (74), 10.27 (44), 10.54 (41), 10.89 (44), 11.46 (49), 11.84 (50), 12.79 (50), 13.03 (47), 13.40 (48), 14.54 (44).

A solution of the above obtained hydrochloride (0.5 g., 0.002 mole) in 10 ml. of water was made alkaline with sodium hydroxide. A colorless crystalline precipitate was collected and recrystallized from a mixture of benzene and ligroin (1:3), yielding colorless needles, m.p. 105–108°.

Anal. Calcd. for $C_9H_{15}N_3OS$: C, 50.70; H, 7.04; N, 19.72; S, 15.02. Found: C, 50.64; H, 6.94; N, 20.00, S, 15.33.

2-Methylthio-4-amino-5-isopropoxymethylpyrimidine hydrobromide (VI). 2-Methylthio-4-amino-5-bromomethylpyrimidine hydrobromide (2 g., 0.006 mole) was treated with 50 ml. of boiling isopropyl alcohol in the same way as the previous experiment, yielding 1.1 g. of colorless needles, which did not melt below 300°.

Anal. Calcd. for $C_9H_{16}BrN_3OS$: Br, 27.16. Found: Br, 27.96.

A solution of this hydrobromide (0.5 g., 0.0017 mole) in 10 ml. of water was made alkaline with sodium hydroxide. The resulting colorless crystals were collected and recrystallized from a mixture of benzene and ligroin (1:3); m.p. 105–108°. No melting point depression was observed on admixture with the sample obtained from the hydrochloride.

2-Methylthio-4-amino-5-methoxymethylpyrimidine hydrobromide. 2-Methylthio-4-amino-5-bromomethylpyrimidine (10 g., 0.015 mole) was added to a solution of 4.5 g. (0.03 mole) of 4-methyl-5-(β-hydroxyethyl)thiazole in 100 ml. of methanol, and the mixture was heated at 55–65° for 12 hr., after which the solution was concentrated to 30 ml. After cooling, white crystals were collected and washed with dry ether; yield, 10.2 g. These crystals were reprecipitated by dissolving in 20 ml. of hot methanol, adding 10 ml. of dry ether, and cooling, m.p. 167–168° (dec.).

Anal. Calcd. for $C_7H_{12}BrN_3OS$: Br, 30.02. Found: Br, 30.13.

When 0.5 g. of the product was dissolved in 10 ml. of water and the solution was made weakly alkaline with sodium hydroxide, colorless crystals, m.p. 104–106°, were collected. These were identified as 2-methylthio-4-amino-5-methoxymethylpyrimidine by mixed melting point.

PHILADELPHIA, PA.

[CONTRIBUTION FROM THE INSTITUTO DE QUÍMICA AGRÍCOLA, MINISTÉRIO DA AGRICULTURA]

The Chemistry of Rosewood. III. Isolation of 5,6-Dehydrokavain and 4-Methoxyparacotoin from *Aniba firmula* Mez

OTTO RICHARD GOTTLIEB AND WALTER B. MORS

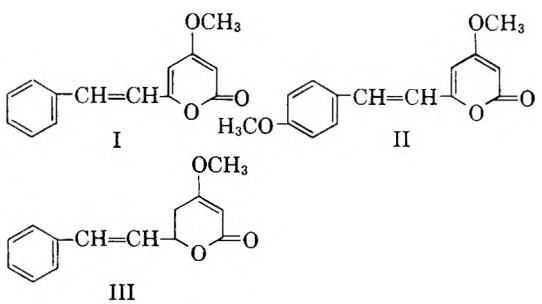
Received August 19, 1958

From the wood of *Aniba firmula* Mez there were isolated benzoic acid, 4-methoxy-6-piperonyl-α-pyrone (4-methoxyparacotoin) and 4-methoxy-6-(β-styryl)-α-pyrone (5,6-dehydrokavain). This latter compound, isolated for the first time from a natural source, has been known by synthesis since 1939. The relationship to the previously described arylpyrones from other plants of the same genus and to the styrylpyrones from *kava* root is pointed out.

Aniba firmula (Nees et Mart.) Mez (family *Lauraceae*) is a tree closely related to the two species of rosewood studied in former articles.[1,2] Its wood is fragrant and finds use in popular perfumery. Although it is not commercially exploited for the production of essential oil, it is sometimes called *louro rosa* (rose laurel) due to a certain similarity of its odor with that of true rosewood.[3] Of all *Aniba* species, this has the widest geographical distribution, reaching from the extreme north of South America, over the Brazilian and Peruvian Amazon, as far south as the Brazilian states of Minas Gerais and São Paulo.[4]

The material investigated was collected in the vicinity of Rio de Janeiro. From the benzene extract of the finely ground wood three cystalline substances could be isolated. One was recognized as benzoic acid. The second was found to be identical with 4-methoxyparacotoin, previously described from *Aniba Duckei* Kostermans and *A. rosaeodora* Ducke.[1] The third compound, greenish yellow crystals, $C_{14}H_{12}O_3$, m.p. 138–140°, appeared to be new. Its ultraviolet and infrared spectra were notably similar to those of 4-methoxyparacotoin and anibine.[1] The presence of a δ-lactone ring was therefore assumed likely. In fact, the substance showed reactions in every way analogous to the pyrones from rosewood. Oxidation with permanganate yielded benzoic acid; when boiled with alkali, cinnamic acid resulted. At room temperature, the compound dissolved in ethanolic potassium hydroxide and from the yellow solution crystals of a dipotassium salt slowly separated out. The infrared spectrum of this salt closely resembles that of the analogous salts from anibine and 4-methoxyparacotoin; the formation of all these salts takes place with loss of the methoxyl group present in the original compounds. Acidification of the potassium salt yielded a yellow degradation product, $C_{12}H_{12}O_2$, m.p. 85°. This was evidently a product of decarboxylation, as indicated not only by the molecular formula, but also by the infrared spectrum, which was again similar to those of the β-diketones, the corresponding degradation products of the two mentioned pyrones. One characteristic feature in the infrared was a strong band at 6.03 μ, persisting through the whole degradation, and presumably indicating the presence of a carbon-carbon double bond. Subsequently, the degradation product $C_{12}H_{12}O_2$ was identified as cinnamoylacetone by comparison with a synthetic specimen.

These data allow the establishment of structure I, 4-methoxy-6-(β-styryl)-α-pyrone, for the new compound from *Aniba firmula*.



I II

III

A search of the literature showed that the formulated substance had been synthesized by Z. Maciorewicz in 1939.[5] Through the courtesy of Dr. Stefania Drabarek, University of Warsaw, we came into possession of a sample of the synthetic compound. The two substances proved to be identical.

This substance, now isolated for the first time from a natural source, is related not only to the

(1) W. B. Mors, O. R. Gottlieb, and C. Djerassi, *J. Am. Chem. Soc.*, **79**, 4507 (1957).

(2) O. R. Gottlieb and W. B. Mors, *J. Am. Chem. Soc.*, **80**, 2263 (1958).

(3) Other popular names are *canela rosa* and *canela sassafrás*. This latter name should not be confused with the North American sassafras, *Sassafras albidum* (Nutt.) Nees, nor with the Brazilian sassafras of commerce, *Ocotea pretiosa* (Nees) Mez, which belong to the same family. *Aniba fragrans* Ducke (popular name *macacaporanga*), a species restricted to a small area in the Lower Amazon Basin [A. Ducke, *Arq. Jard. Bot. Rio de Janeiro*, **4**, 189 (1925); *Anais da Primeira Reunião Sul-Americana de Botânica (Rio de Janeiro)*, **3**, 59 (1938)], is considered by Kostermans to be identical with *A. firmula*. A chemical examination of this disputed species is planned.

(4) A. J. G. H. Kostermans, Revision of the *Lauraceae*. *V., Rec. trav. bot. neerl.*, **35**, 921 (1938). Recently material has been collected even in the state of Santa Catarina (I. de Vattimo, private communication).

(5) Z. Maciorewicz, *Sprawozdania Posiedzén Towarz. Nauk. Warszaw. Wydz'at III. Nauk. Mat. Fiz.*, **32**, 37 (1939); *Roczniki Chem.*, **24**, 144 (1950).

arylpyrones from rosewood and the *coto* barks,[1] but also to the styrylypyrone yangonin (II)[6] and the styryldihydropyrones methysticin[7] and kavain (III)[8] from *kava* root (*Piper methysticum* Forst., family *Piperaceae*). Thus I becomes 5,6-dehydrokavain.

EXPERIMENTAL[9]

Extraction procedure. The wood was reduced to sawdust and then extracted exhaustively with benzene in a Soxhlet apparatus. After concentration, a small quantity of basic material was removed with dilute hydrochloric acid.

Benzoic acid. The benzene solution was next extracted several times with aqueous sodium bicarbonate. Acidification yielded a precipitate which was separated and dried. Vacuum sublimation yielded colorless crystals, m.p. 121–122°, identified as benzoic acid by mixture melting point and infrared spectral comparison with an authentic sample.

A small additional amount of acidic material was extracted with 3% aqueous sodium hydroxide, but was not further investigated.

Essential oil. The remaining benzene solution was evaporated and the semisolid residue exhaustively extracted with boiling petroleum ether. This procedure removed an essential oil in 1.3% yield calculated on the extracted wood.

5,6-Dehydrokavain (I) *and 4-methoxyparacotoin.* The residue insoluble in petroleum ether was dissolved in benzene and chromatographed on alkaline alumina. Elution with benzene yielded first 5,6-dehydrokavain (I) (yield 0.5%) and subsequently 4-methoxyparacotoin (yield 0.2%). The latter substance was crystallized from ethanol. Colorless needles, m.p. 222–224°. Its identity was established by comparison (mixture melting point and infrared spectrum) with a specimen of 4-methoxyparacotoin from *Aniba Duckei*.

Compound (I) was crystallized from ethanol and purified by sublimation *in vacuo*. Greenish yellow crystals, m.p. 138–140°, $[\alpha]_D$ 0° (c, 4 in $CHCl_3$,c); $\lambda_{max}^{CHCl_3}$ 5.80, 6.02, 6.15, 6.38μ; λ_{max}^{EtOH} 230 mμ (log ϵ 4.13), 255 mμ (log ϵ 4.10), 343 mμ (log ϵ 4.37); λ_{min}^{EtOH} 245 mμ (log ϵ 3.92), 275 mμ (log ϵ 3.72).

Anal. Calcd. for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30; one OCH_3, 13.60. Found: C, 73.18; H, 5.20; OCH_3, 13.71.

Oxidation of 5,6-dehydrokavain (I) (123 mg.) with potassium permanganate in acetone at room temperature yielded benzoic acid (40 mg.), purified by vacuum sublimation, m.p. 122°, identified by mixture melting point and infrared spectral comparison with an authentic sample.

Alkaline cleavage of 5,6-dehydrokavain (I). (*a*) *With boiling alkali.* A solution of 198 mg. of 5,6-dehydrokavain (I) in 20 ml. of 0.5 *N* aqueous ethanolic potassium hydroxide were heated under reflux for 3 hr. After dilution with water, chloroform removed 75 mg. of an oil. The liquid was then acidified and again extracted with chloroform. Evaporation of the solvent left 44 mg. of a slightly yellow, crystalline mass. Recrystallization from petroleum ether–chloroform (1:1) and subsequent sublimation *in vacuo* yielded colorless crystals of cinnamic acid, m.p. 131–133°, proved to be identical by mixture melting point determination and infrared comparison with an authentic specimen.

(*b*) *At room temperature.* A solution of 200 mg. of 5,6-dehydrokavain (I) was left at room temperature in 35 ml. of 1*N* ethanolic potassium hydroxide. After 2 hr., crystals began separating out, increasing slowly in quantity with time. They were filtered off after 18 hr. and washed with absolute ethanol yielding 104 mg. yellow crystals, m.p. 230° dec.; λ_{max}^{Nujol} 6.04, 6.23μ.

Anal. Calcd. for $C_{13}H_{10}O_4K_2$: K, 25.36. Found: K, 26.11; OCH_3, 0.00.

Acid degradation. A solution of 250 mg. of the potassium salt in 5 ml. of water was acidified with a few drops of hydrochloric acid. The resulting yellow precipitate (96 mg.) of cinnamoylacetone was filtered and crystallized from aqueous ethanol affording yellow crystals, m.p. 85°. $\lambda_{max}^{CHCl_3}$ 6.02, 5.28μ.

Anal. Calcd. for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.07; H, 6.46.

Identity with a synthetic specimen of cinnamoylacetone prepared by condensation of ethyl cinnamate and acetone in ether solution in the presence of sodium,[10] was established by direct comparison (mixture melting point and infrared spectrum).

Comparison of natural and synthetic 5,6-dehydrokavain. Mixture melting point determination showed no depression and the ultraviolet and infrared spectra of the two samples were superimposable.

Acknowledgments. We wish to pay tribute to the late Dr. J. G. Kuhlmann, notable Brazilian botanist, who did not live to see this work concluded. Our first material of *Aniba firmula* was collected at his suggestion and was identified by him. We are also grateful to Dr. Paulo Agostinho Matos Araujo, chief of the Section of Wood Technology, Forest Service, Ministry of Agriculture, who supplied us with additional wood samples. Recognition is due to Dr. Ida de Vattimo, Botanical Garden, Rio de Janeiro, for her orientation in the botanical aspects pertaining to the family *Lauraceae*. We are indebted to Dr. Stefania Drabarek, University Warsaw, for a generous sample of synthetic 4-methoxy-6-(β-styryl)-α-pyrone as well as for reprints of the Polish papers. Finally, we wish to express our appreciation to the Conselho Nacional de Pesquisas, Brazil, for financial aid.

RIO DE JANEIRO, BRAZIL

(6) I. Chmielewska and J. Cieślak, *Roczniki Chem.*, **28**, 38 (1954).

(7) W. Borsche, C. H. Meyer, and W. Peitzsch, *Ber.*, **60**, 2113 (1927).

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(9) All melting points were determined on the Kofler block. Ultraviolet spectral measurements were performed with a Beckman model DU spectrophotometer. We are indebted to Mrs. Dolores Phillips and Miss Birgitte Bach, Spectrophotometric Laboratory, Wayne State University, Detroit, Mich., for the infrared spectral measurements and to Dr. A. Bernhardt, Mühlheim, Germany, for the microanalyses.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DEFENSE ACADEMY]

A New Barbituric Acid Synthesis in Liquid Ammonia-Alkali Hydroxide. II.[1] Condensation of Malonamide Derivatives with Ethyl Carbonate

KOTARO SHIMO AND SHIGERU WAKAMATSU

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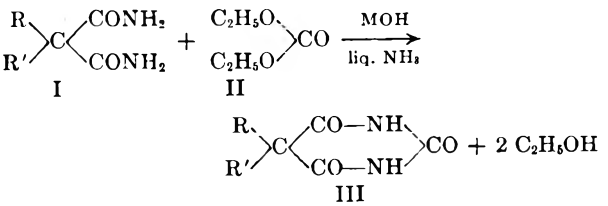
A new synthesis of barbituric acid derivatives has been devised. It was found that ethyl carbonate could be condensed readily with malonamide or its *C*-alkylated derivatives by using sodium hydroxide as the condensing agent in liquid ammonia. The effect on yield of variations in the reaction conditions was also studied.

The *C*-alkyl- and *C*, *C*-dialkyl-malonamides required in this investigation were successfully prepared by the alkylation of malonamide using sodium hydroxide in liquid ammonia. Six alkylated malonamides, two of these new, were prepared in excellent yields by this method.

A number of barbituric acid syntheses have been described in the literature. For example, malonic acid, as well as *C*-substituted malonic acids, have been condensed with urea. Urea has also been treated with malonyl and substituted malonyl chlorides. In addition malonamide has been treated with phosgene and *C*,*C*-dialkylmalonamides have been condensed with alkyl or phenyl carbonate. However, by far the most common procedure used in preparing barbituric acids is that based on the method of Michael,[2] namely, the condensation of urea with the appropriate diethyl malonate in the presence of sodium ethoxide in anhydrous alcohol. This is the method which has been generally adopted for the industrial production of barbituric acids and also represents the most common laboratory preparative procedure.

In a recent paper[1] we outlined a modification of the usual barbituric acid synthesis which used an alkali hydroxide as the condensing agent and liquid ammonia as the solvent. According to this procedure the diethyl dialkylmalonate, urea and an alkali hydroxide were dissolved or suspended in liquid ammonia and the mixture well agitated for about an hour in a pressure flask at room temperature. Dialkylbarbituric acids were produced in 50–60% yield. However, when diethyl malonate or monoalkylated diethyl malonates were tried none of the desired barbituric acids could be isolated.

The present investigation is concerned chiefly with still another approach to barbituric acid synthesis. We have now found that malonamides (I) condense readily with ethyl carbonate (II) in



Where R, R′ = H, alkyl, allyl, etc.

liquid ammonia in the presence of an alkali hydroxide or alkali amide. The reaction appears to be quite general, giving good yields of barbituric acids (III) with malonamide, *C*-alkylmalonamides or *C*,*C*-dialkylmalonamides. The yields obtained for six representative barbituric acids are shown in Table I. Also listed are the results of a study comparing the effect of various alkaline condensing agents on these yields. It will be noted that sodium hydroxide gave the most uniformly good results of any of the condensing agents used. *C*,*C*-Dialkylmalonamides have been condensed with alkyl or phenyl carbonate in the presence of alkali alcoholate in alcohol,[3] and also of alkali metal, alkali alcoholate or alkali amide without solvent.[4] The using of malonamide or *C*-alkylmalonamide in the reactions have never been described.

The *C*-alkyl and *C*,*C*-dialkylmalonamides used in the present investigation were prepared according to a new method recently described by Asami and Shimo.[5] According to this procedure malonamide was alkylated using an alkali hydroxide in liquid ammonia at room temperature in a pressure flask. In the present work some improvements have been made in the synthesis of dialkylmalonamides, especially in the case of single step diallylation. It was found that this reaction was best carried out at atmospheric pressure and yielded more than 80% of diallylmalonamide from malonamide and two molar equivalents each of allyl bromide and sodium hydroxide in liquid ammonia. On the other hand, when the reaction was run under pressure at room temperature none of the desired diallyl derivative was obtained.

EXPERIMENTAL

Reagents. Malonamide was obtained by the ammonolysis of ethyl malonate in liquid ammonia[6]; m.p. 167–168.5°.

(1) For the first paper in this series see K. Shimo and S. Wakamatsu, *J. Chem. Soc. Japan (Ind. Chem. Sect.)*, **60**, 1141 (1957).

(2) A. Michael, *J. prakt. Chem.*, (2) **35**, 449 (1887).

(3) Friedr. Bayer & Co., German Patent **163,136**, *Chem. Zentr.* 1905 II, 1141.

(4) Friedr. Bayer & Co., German Patent **168,406**, *Chem. Zentr.*, 1906 I, 1200.

(5) R. Asami and K. Shimo, *J. Chem. Soc. Japan (Ind. Chem. Sect.)*, **60**, 1034 (1957).

TABLE I

SYNTHESIS OF BARBITURIC ACIDS BY CONDENSATION OF MALONAMIDES WITH ETHYL CARBONATE IN LIQUID AMMONIA

$RR'C(CONH_2)_2$ R–	R'–	Condensing Agent[a]	Hours Shaken[b]	Product Barbituric Acid	Yield,[c] %	Malonamide Recovered[d]
H	H	NaOH	3		56	..
H	H	KOH	3,5		56	..
H	H	KNH_2	3		47	..
H	Ethyl	NaOH	1	Ethyl-	44	..
H	Ethyl	$NaNH_2$	1	Ethyl-	38	..
H	Ethyl	KNH_2	1	Ethyl-	36	
H	*i*-Amyl	NaOH	0,5	*i*-Amyl-	78(100)	22
H	*i*-Amyl	KOH	3	*i*-Amyl-	66(80)	17
H	*i*-Amyl	KNH_2	3	*i*-Amyl-	51(66)	22
Ethyl	Ethyl	NaOH	3	Diethyl-	35(77)	54
Ethyl	Ethyl	KOH	3	Diethyl-	14(47)	70
Ethyl	Ethyl	$NaNH_2$	4	Diethyl-	27(68)	60
Allyl	Allyl	NaOH	3	Diallyl-	82(95)	14
Allyl	Allyl	KOH	3	Diallyl-	65(93)	30
Allyl	Allyl	$NaNH_2$	3	Diallyl-	55(98)	44
Ethyl	*i*-Amyl	NaOH	5	Ethyl *i*-Amyl	40(100)	60
Ethyl	*i*-Amyl	KOH	5	Ethyl *i*-Amyl	4(100)	96
Ethyl	*i*-Amyl	$NaNH_2$	5	Ethyl *i*-Amyl	29(100)	71

[a] Approximately two molar equivalents of alkaline condensing agent were used per mole of $RR'C(CONH_2)_2$. When the ratio was either greater or less, yields were lowered appreciably. [b] The reaction mixtures were shaken continually at room temperatures for the period of time specified. Apparently the time element was not critical for periods ranging from 0.5 to 5 hours did not affect the yields significantly. [c] Yields based on the starting malonamides. Parenthesized figures indicate the yields calculated on the basis of the actual malonamide consumed. [d] Based on starting malonamides.

The commercially available ethyl carbonate was used; b.p. 124–126°. Sodium and potassium hydroxides were the commercial granulated products; purity, evaluated by the neutralization method, 93% and 87% respectively. The liquid ammonia was the commercial product once distilled in a bomb.

Syntheses of malonamide derivatives. Essentially two methods of alkylation were employed; (I) the use of a pressure vessel at room temperature and (II) the reaction at atmospheric pressure at the temperature of liquid ammonia (−33°). These are illustrated by the preparation of ethylmalonamide (Method I) and diethylmalonamide (Method II).

2-Ethylmalonamide (Method I). Malonamide (5.1 g.) (0.05 mole), 2.2 g. (approx. 0.05 mole) of sodium hydroxide and about 50 cc. of liquid ammonia were placed in a glass pressure vessel (Fig. 1). The mixture was shaken for 0.5 to 1 hr. at room temperature until the metallation was complete as indicated by the disappearance of the solid sodium hydroxide. To the mixture was then added 6 g. (0.055 mole) of ethyl bromide and the shaking continued for 1 to 2 hr. After evaporation of the ammonia the remaining solids were washed with cold water; yield, 4.6 g. (71%) of 2-ethylmalonamide; m.p. 209.2–211.5°. Conrad and Schulze[7] prepared this compound in 40% yield by the alkylation of malonamide using ethyl iodide as the alkylating agent and sodium methoxide as the condensing agent. We have almost doubled the yield by our new variation of this synthesis.

2,2-Diethylmalonamide (Method II). In a well cooled (below −33°) one-liter three-necked flask provided with an efficient mercury sealed stirrer and a Dewar reflux condenser, protected by a soda-lime tube, were placed about 350 cc. of liquid ammonia and 11 g. (0.2 mole) of potassium

Fig. 1. Reaction vessel

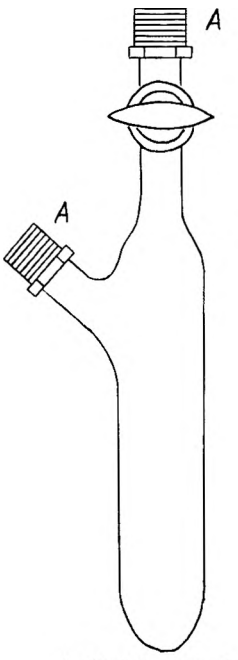
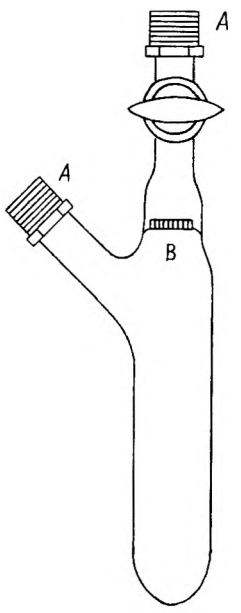


Fig. 2. Reaction vessel with glass filter



A. Stainless steel joint. B. Glass filter

amide.[8] While stirring vigorously, 26 g. (0.2 mole) of ethylmalonamide was added which formed potassioethylmalonamide. This was followed by the dropwise addition of 24 g. (0.22 mole) of ethyl bromide over the period of an hour. After an additional two hours of stirring the ammonia was evaporated and the remaining solids washed with water and then recrystallized from water; yield 21.2 g. (67%) of 2,2-diethylmalonamide which melted at 218–219.5°. This com-

(6) K. Shimo and R. Asami, *J. Chem. Soc. Japan (Pure Chem. Sect.)*, **78**, 800 (1957), reported that a 97% yield of malonamide resulted by allowing a mixture of ethyl malonate and liquid ammonia (1:5.7 molar ratio) to stand at room temperature for four days. In the present work we added 10% of ammonium chloride (on a molar basis as compared to ethyl malonate) as a catalyst and thereby completed the reaction within 24 hr.

(7) M. Conrad and A. Schulze, *Ber.*, **42**, 729 (1909).

(8) K. W. Greenlee and A. L. Henne, *Inorg. Syntheses*, **2**, 135 (1946).

pound has been prepared previously by the ammonolysis of 2,2-diethylmalonyl chloride[9] or diethyl 2,2-diethylmalonate.[10]

2-Isoamylmalonamide was prepared in 89% yield by Method I using isoamyl iodide as the alkylating agent; m.p. 219.5–220.5°, after recrystallization from dilute alcohol.

Anal. Calcd. for $C_8H_{16}N_2O_2$: C, 55.81; H, 9.30; N, 16.28. Found: C, 55.76; H, 9.23; N, 16.35.

Hoffman[11] reported a melting point of 210° for this compound which he prepared by the ammonolysis of the corresponding diethyl ester in a closed tube.

2-Allylmalonamide (Method II). A 65% yield was obtained from malonamide and allyl bromide using sodium hydroxide as the condensing agent. After recrystallization from alcohol the product melted at 167°.

Anal. Calcd. for $C_6H_{10}N_2O_2$: N, 19.72. Found: N, 20.15.

2,2-Diallylmalonamide. This compound was synthesized in 66% yield from allylmalonamide and allyl bromide (Method I). The crude product melted at 194–199°. Using Method II, with potassium amide as the condensing agent, the yield was increased to 90% and the melting point raised to 201–202°.

The introduction of both allyl groups in a single step was achieved in 81% yield (Method II) by starting with malonamide and using two molar equivalent each of allyl bromide and sodium hydroxide; m.p. 198–200.5° (crude product). Meyer[12] prepared this compound by the ammonolysis of the corresponding dimethyl ester.

2-Ethyl-2-isoamylmalonamide (Method I) was prepared in 55% yield from ethylmalonamide and isoamyl iodide using sodium hydroxide as the condensing agent. The yield increased to 75% when potassium amide (prepared in the reaction vessel indicated in Fig. 2)[13] was used. The product, after recrystallization from dilute alcohol, melted at 191–192.5°.

Anal. Calcd. for $C_{10}H_{20}N_2O_2$: C, 60.00; H, 10.00; N, 14.00. Found: C, 59.82; H, 10.09; N, 13.77.

Synthesis of barbituric acid derivatives. In general the best results were obtained when the reactants were used in the approximate ratio of one mole of the appropriate malonamide to 1.3 moles of ethyl carbonate and 2 moles of an alkali hydroxide[14] or alkali amide. The following two examples represent typical procedures.

Barbituric acid. In a glass pressure vessel were placed 1.28 g. (0.0125 mole) of malonamide, 2. g. (0.017 mole) of ethyl carbonate, 1.1 g. (0.025 mole) of sodium hydroxide and 10–25 ml. of liquid ammonia. The mixture was then shaken at room temperature. In a moment most of the sodium hydroxide had disappeared and a brown precipitate (sodium barbiturate) began to separate. After 3 hr. the ammonia was evaporated off and the product, along with the easily soluble unreacted malonamide, was extracted with water. Neutralization of the extract with 50% sulfuric acid gave fine crystals of barbituric acid; yield 0.9 g. (56%), m.p. 243–244° (crude product).

5,5-Diallylbarbituric acid. A mixture of 1.82 g. (0.01 mole) of 2,2-diallylmalonamide, 1.5 g. (0.0127 mole) of ethyl carbonate, 0.9 g. (0.02 mole) of sodium hydroxide and 25 cc. of liquid ammonia was placed in a glass pressure vessel. After shaking for about 0.5 hr. at room temperature the reaction was substantially complete. The reaction was allowed to shake for a total of 3 hr. and then the ammonia removed. The sodium salt of the reaction product was extracted with water. Since the unreacted 2,2-diallylmalonamide was practically water insoluble it could be quantitatively recovered. Neutralization of the aqueous extract with concentrated hydrochloric acid precipitated the fine crystals of 5,5-diallylbarbituric acid; yield, 1.7 g. (82% based on starting amide). After recrystallization from water it melted at 171°.

YOKOSUKA, JAPAN

(9) K. Böttcher, *Ber.*, **39**, 1596 (1906).

(10) B. Russell, *J. Am. Chem. Soc.*, **72**, 1853 (1950).

(11) P. Hoffman, *Ber.*, **23**, 1498 (1890).

(12) H. Meyer, *Monatsh.*, **27**, 1091 (1906).

(13) Potassium amide was readily prepared in the reaction vessel pictured in Fig. 2 and filtered directly into the reaction mixture through the fitted glass filter. However, sodium amide, being insoluble in ammonia, could not be prepared in the same fashion so was used directly as a suspension.

(14) The particle size of the commercial granulated product was reduced in a mortar before use.

[CONTRIBUTION FROM THE WESTINGHOUSE RESEARCH LABORATORIES]

Methylene Bridge Formation *via* Carbonium Ions in the Phenol-Formaldehyde Reaction

JACOB S. RODIA AND JAMES H. FREEMAN

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Polyphenylmethylene structures are accepted as the principal component of polymers derived from the reaction of phenol and formaldehyde. The reaction between methylolphenol or halomethylphenol compounds and phenols to yield dihydroxydiphenylmethanes is interpreted in terms of a common, hydroxy substituted, benzyl cation intermediate. Experimental evidence in support of this intermediate is presented for the first time. In terms of this mechanism dibenzyl ether formation is viewed as a competing reaction which may predominate under special conditions. A case of preferential reaction between a hydroxybenzyl cation and an aromatic hydrocarbon is presented in which a phenol, although present, failed to react.

Reaction between phenol and formaldehyde to give resins is now well recognized to proceed stepwise.[1–5] There is first an addition of formaldehyde to phenol to give methylolphenols and second, a condensation of methylolphenol compounds with other phenols to form polymers joined predomi-

(1) R. W. Martin, *Chemistry of Phenolic Resins*, J. Wiley and Sons, New York (1956).

(2) K. Hultzsch, *Chemie der Phenolharze*, Springer Verlag, Berlin (1950).

(3) J. F. Walker, *Formaldehyde*, 2nd ed., Chap. 12, Reinhold Corp., New York (1953).

(4) A. Zinke, *J. Appl. Chem.*, **1**, 257 (1951).

(5) M. Imoto, *J. Inst. Polytechn., Osaka*, 2, (2) Series C (1952).

nately by methylene bridges and termed hydroxyphenylmethanes.

The reaction of suitable ring substituted methylolphenol derivatives with other substituted phenols is an important tool for the synthesis of representative intermediate compounds of unequivocal structure.[6-10] Such blocked phenols also were employed by many prior investigators[4, 11-15] for the purpose of permitting isolation of intermediate substances by reducing the number of possible isomers. Although at times criticized[16,17] as not necessarily representative of what happens when such trireactive compounds as phenol itself or *m*-cresol are used, experiments of this type did provide knowledge of what reactions might occur under given conditions. What actually happens with the commercially important phenols will be, of course, the result of the relative attractiveness (as determined by concentration and reaction rates) of the several alternate paths available under the environmental conditions at any given stage of polymerization.

Since the reaction is much used and of considerable importance from both a theoretical and practical standpoint, possible mechanisms by which it may proceed have been suggested by several workers. For example, Hultzsch[18] postulated formation of a quinone methide intermediate (formed by internal loss of water from a methylolphenol) which then, in an ionic form, attacked another phenol nucleus at positions of highest electron density to establish the methylene bridge.

Ziegler,[11-13] envisioned conversion of methylolphenols to halomethylphenols when halogen acids were used as catalysts. He and his coworkers advanced the successful reaction between a halomethylphenol and a phenol giving a diphenylmethane as experimental support for this theory. However, the fact that he was able to convert a methylolphenol to a chloromethylphenol in the presence of excess strong hydrochloric acid, and that chloromethylphenols can react with phenols to form diphenylolmethanes are not, *per se*, conclusive proof that the halomethylphenol is an actual intermediate in the conversion of methylolphenol to diphenylmethane. It is more difficult to envision the mixed ester as intermediate in cases where other acids such as sulfuric, *p*-toluenesulfonic, perchloric, etc. are used as catalysts, particularly in dilute form, yet these are known to promote the reaction in question.

It would also follow that a presynthesized halomethylphenol should therefore condense with a phenol in absence of a catalyst. Our attempts to employ this principle in the preparation of 3,3′,5,5′-tetrabromo-2,4′-dihydroxydiphenylmethane by reaction between 3,5-dibromo-2-hydroxybenzyl bromide and 2,6-dibromophenol resulted in a complete failure to react in the absence of catalyst. Similar difficulties in carrying out the reaction when a halogen substituted (therefore less reactive) addend is used had also been reported by Finn and Lewis.[9] On the other hand Yamazaki[19] has reported successful formation of the diphenylmethane from a melt of 2,6-dichloro-4-hydroxymethylphenol and *p*-bromophenol using a trace of perchloric acid as catalyst. In our experiment the reaction also proceeded smoothly to methylene bridged compound when only a trace of catalyst (H^+ion) was added.

Pepper[20] and Lilley[16] independently have proposed a mechanism for diphenylmethane formation from phenol alcohols which involves a benzyl cation as the active intermediate. Lilley further expanded this view to explain benzyl ether formation but neither of these authors was able to furnish substantial experimental data to support it. Imoto[5] also regards the reaction intermediate to be the benzyl cation on the basis of his consideration of relative kinetic rates and activation energies for the methylol addition and condensation steps respectively. Likewise Dewar[21] in his textbook *The Electronic Theory of Organic Chemistry* depicts an interesting mechanistic analogy between the phenol-formaldehyde condensation and a Friedel-Crafts reaction. Unfortunately references and experimental data are again lacking.

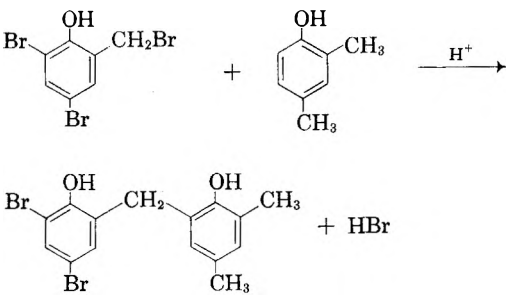
The authors reasoned that if methylene bridges in phenolic resins occur *via* a benzyl cation then reagents and conditions known to produce such ions[22] (*i.e.*, reaction of silver salts with alkyl halides) should be capable of catalyzing a reaction between a halomethylphenol and another phenol. This was found to be the case as evidenced by successful reaction between 3,5-dibromo-2-hydroxybenzyl bromide and 2,6-dichlorophenol, employing a molecular equivalent of silver perchlorate as promoter and nitromethane as solvent. When less than one

(6) A. C. Davis, B. T. Hayes, and R. F. Hunter, *J. Appl. Chem.*, **7**, 521 (1957).
(7) S. R. Finn, J. W. James, and C. J. S. Standen, *J. Appl. Chem.*, **4**, 296 (1954).
(8) S. R. Finn, J. W. James, and C. J. S. Standen, *J. Appl. Chem.*, **4**, 497 (1954).
(9) S. R. Finn and G. J. Lewis, *J. Appl. Chem.*, **1**, 560 (1951).
(10) W. J. Burke, W. E. Craven, A. Rosenthal, S. H. Ruetman, C. W. Stephens, and C. Weatherbee, *J. Polymer Sci.*, **20**, 75 (1956).
(11) E. Ziegler, *Ost. Chem. Ztg.*, **49**, 92 (1948).
(12) E. Ziegler, *Monatsh.*, **78**, 334 (1947).
(13) E. Ziegler, *Monatsh.*, **79**, 142 (1948).
(14) H. v. Euler, E. Adler, J. O. Cedwall, and O. Törngren, *Arkiv. Kemi. Min. Geol.*, **15A** (11) (1941).
(15) K. Hultzsch, *Kunst.*, **32**, 69 (1942); **37**, 205 (1947).
(16) H. S. Lilley, *J. Soc. Chem. Ind.*, **67**, 196 (1948).
(17) E. G. K. Pritchett, *Chem. and Ind. (London)*, 295 (1949).
(18) K. Hultzsch, *Angew. Chem.*, **61**, 93 (1949).
(19) T. Yamazaki, *J. Ind. Chem., Japan*, **58**, (12) 972 (1955).
(20) D. C. Pepper, *Chem. and Ind. (London)*, 866 (1941).
(21) M. J. S. Dewar, *Electronic Theory of Organic Chemistry*, Oxford University Press, London, 180 (1949).
(22) E. R. Alexander, *Ionic Organic Reactions*, Chap. 3 J. Wiley & Sons, New York (1950).

equivalent of silver perchlorate was used, the reaction stopped short of completion. The silver halide formed precipitated from the solution and further generation of the carbonium ion was prevented. We also repeated the experiment of Finn and Lewis[9] and confirmed the inability of 3,5-dibromo-4-hydroxybenzyl bromide to condense with *p*-bromophenol even with use of an acid catalyst. However, we were able to bring about a successful reaction between these reagents in nitromethane solution using silver perchlorate (one equivalent) as catalyst.

Additional support for the carbonium ion theory was obtained by an experiment in which toluene was substituted for nitromethane as solvent. In this case the main product of the reaction was found to be a methyl, monohydroxydiphenylmethane produced by reaction between the benzyl halide and toluene. The phenyl nucleus in toluene is sufficiently activated by the presence of the methyl group to permit it to act as the addend for the benzyl cation and its relatively high concentration completely swamped the reaction potential of the normally reactive ring position in the phenol. The latter in this case is handicapped further by the ring deactivating inductive effect of the 2 6-halogen atoms.

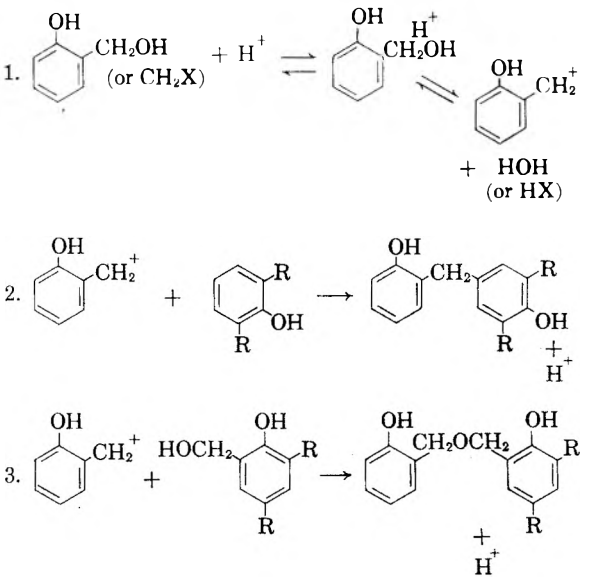
In cases where the addend is of enhanced reactivity *i.e.* contains ring positions of relatively increased electron density, due to the presence of substituent groups as the methyl group, instead of deactivated as by halogen, the relative yield of diphenylolmethane is increased and the reaction conditions are correspondingly less severe. Thus, 3,5-dibromo-2-hydroxybenzyl bromide combines readily with 2,4-dimethylphenol, though only indifferently with 2,6-dihalophenols.



It would also be expected that the relative ease of formation of the benzyl cation would have a bearing on the success of the reaction. In this respect it appears qualitatively easier to form such a carbonium ion from the hydroxymethyl group by protonation and release of HOH than it is to eliminate the corresponding HX moity from the halomethyl compound. This result is consistent with the relative hydrogen bond forming power of halogen and hydroxy groups.[23]

(23) L. Pauling, *Nature of the Chemical Bond*, 2nd ed., Cornell University Press, Ithaca, N. Y., 1940, p. 287.

The benzyl cation which we postulate as common intermediate in the reaction of methylolphenols or halomethylphenols can be considered to arise readily from the reversible solvation of a proton by the benzylic hydroxyl group. The phenolic hydroxyl group as well as the solvent (water in most cases) will, of course, compete reversibly for protons, but the benzyl alcohol group is capable of a further reaction—loss of a stable small molecule (H_2O or HX) and formation of the benzyl cation. (Equation 1.) The reaction may then be propagated in several fashions by reacting with any substance HA which will regenerate the proton.



The presence of carbonium ion in neutral or acidic medium is thus capable of accounting for the conversion of methylolphenol to dibenzyl ether (Equation 3.) as well as to diphenylmethane (Equation 2.). The available protons will be distributed randomly through the system among water molecules, methylol and phenolic hydroxyl groups. Not all the methylol groups will be protonated—hence able to form carbonium ion, simultaneously. Methylol groups which are not in the carbonium ion state will act as electron centers and compete with unsubstituted ring positions as loci for the attachment of the carbonium ion. Elimination of a proton allows the reaction to continue and leaves as product the dibenzyl ether (Equation 3.).

It is to be expected that the free methylol groups will compete best when their number is great in proportion to the number which have been sacrificed to produce benzyl carbonium ions. Thus, ethers should form most readily in nearly neutral solutions and, in fact, this is where most evidence for ether formation has been adduced. In particular cases, competition of free ring positions is eliminated by special circumstances. If active positions are blocked by non-reactive substituents, or if complete methylolation has occurred, as in trimethylol-

phenol,[24] the methylol is the only available target for the carbonium ion and ethers can be expected under very mild conditions. This is aptly demonstrated by our isolation of a 44% yield of dibenzyl ether by trituration of a blocked methylol phenol with dilute hydrochloric acid at room temperature. The ready reaction between highly methylolated phenols and alcohols or glycols[25,26] to give alkylbenzyl ethers is also in accord with this mechanism. Similar cases of ether formation when the electron density at ring positions is reduced, relative to the methylol hydroxyl groups, by presence of chloro or nitro groups have been reported.[27] When it is considered that none of his compounds contained any free *ortho-* or *para-*ring positions capable of reacting with a methylol group to form a methylene bridged compound, the extensive work of Ziegler[11–13,28] is explainable as well on the basis of the carbonium ion theory as it is on the premise of the halomethyl intermediate. His findings can likewise be used to support our conclusions. With high concentrations of both chloride and carbonium ion, isolation of the halomethyl phenol is to be expected. In our view it is regarded as a by-product rather than an intermediate of the reaction.

Since the phenolic hydroxyl group is also capable of solvating protons, it will be present to an extent as $ArOH_2^+$. The benzyl carbonium ion likewise carries a positive charge and the mutual repulsion of these charges may provide an indication of why the *para-* position of a phenol seems to be a favored point of condensation although two *ortho-* positions are available. The preferred orientation toward the *para-* position would be a maximum at very low *p*H values and be less effective as *p*H rises. It has already been reported that the percent of *ortho-* linked diphenylmethane isomer increases with increasing *p*H.[29]

We may also extend our consideration to the relative reactivity of *para- versus ortho*-methylol groups. Lack of ability of the *p*-methylol moiety to be internally stabilized by formation of intramolecular hydrogen bonds (as found between the *ortho-* methylol and phenolic hydroxyl groups) would render the *para* group more accessible to protons, thus more readily generate carbonium ions, and contribute to the observed greater reactivity of these compounds versus their *ortho-*isomers.[30]

Conclusion. On the basis of the experimental evidence presented it is concluded that under acid conditions methylene bridges in phenolic resins occur *via* a benzyl cation. This ion forms by addition of a proton to the hydroxymethyl or halomethyl group of the intermediate phenolformaldehyde addition product, followed by loss of a stable small molecule such as water. The reaction is propagated by coupling of the ion with a position of high electron density in another molecule and regeneration of a proton. In normal resinification reactions the preferred coupling point is the *ortho-* or *para-* position of another phenolic ring. Benzyl ethers are formed when the circumstances are such that the concentration of available ring positions is low and the concentration of unprotonated methylol groups is high. Other ion engendering agents (as silver salts acting on halomethylphenols) may be used instead of hydrogen ion to generate benzyl carbonium ion in non aqueous media. In a case where carbonium ion was generated in the presence of excess toluene, the product of reaction with the toluene rather than phenol was isolated in good yield.

EXPERIMENTAL

All of the phenols used were high grade commercial products, redistilled or recrystallized as appropriate, except 2,6-dichlorophenol which was prepared from ethyl *p*-hydroxybenzoate by a standard method,[31] m.p. 62°.

3,5-Dibromo 2-hydroxybenzyl bromide (I) was prepared in high yield (85%) by the bromination of saligenin (m.p. 85°) in an ether–chloroform mixture at 5–10°. The product was recrystallized from glacial acetic acid, then from benzene–hexane mixture. M.p. 118.5–119°; m.p. (lit.) 116–118.[32]

3,5,3',5'-Tetrabromo-2,4'-dihydroxydiphenylmethane. Initially we attempted to prepare this compound by reaction between I and 2,6-dibromophenol. Equimolar amounts of the reagents were heated at 140°C. for 12 hr. in a nitrogen atmosphere. Only a negligible amount of hydrogen bromide was evolved and more than 75% of the original benzyl bromide (I) was recovered by recrystallization from benzene. The experiment was repeated with identical results.

Next the experiment was repeated but with the addition of 0.5 g. of *p*-toluenesulfonic acid to a 0.2 mole batch. HBr was evolved. The crude product was recrystallized, first from benzene (with charcoal) and then from glacial acetic acid. A 21% yield of the desired dimer was obtained melting at 195°. Evaporation of the solvents gave a residue which could be separated by extraction with hot petroleum ether into two fractions representing 15% of the original benzyl bromide (I, m.p. 116°) and 50% of the original 2,6-dibromophenol (m.p. 51°).

Greater success was achieved by reaction between 3,5-dibromo-2-hydroxybenzyl alcohol[32] (m.p. 88°) and about 10 mole per cent excess of 2,6-dibromophenol using *p*-toluenesulfonic acid as catalyst. At 140°, under nitrogen, a 56% yield of tetrabromo dihydroxydiphenylmethane was obtained after only 1.5 hr. heating. After two recrystallizations from benzene, the melting point was 196–197°, m.p. (lit.) 199°.[33]

3,5-Dibromo 3',5'-dichloro 2,4'-dihydroxydiphenylmethane (II). Obtained by a similar experiment using 3,5-dibromo 2-hydroxybenzyl alcohol and two equivalents of 2,6-di-

(24) H. Kammerer and M. Grossman, *Angew. Chem.*, **65**, 263 (1953).
(25) W. Krumbhaar, U. S. Patent **2,268,946** (1942).
(26) A. Greth, *Angew. Chem.*, **51**, 719 (1938).
(27) W. Borsche and A. D. Berkhout, *Liebig's Ann.*, **330**, 82 (1904).
(28) G. Zigeuner and E. Ziegler, *Monatsh.*, **79**, 100 (1948).
(29) S. R. Finn and J. W. G. Musty, *J. Soc. Chem. Ind.*, Suppl. Issue No. 2, S.49 (1950).
(30) J. Reese, *Kunst* **45**, 137 (1955).
(31) *Org. Syntheses*, **29**, 35 (1949).
(32) K. von Auwers and G. Büttner, *Liebig's Ann.*, **302**, 131 (1898).
(33) N. J. L. Megson and A. A. Drummond, *J. Soc. Chem. Ind.*, 251T (1930).

chlorophenol with *p*-toluenesulfonic acid as catalyst. After 5 hr. at 140° the excess dichlorophenol was removed by vacuum distillation and the residue recrystallized from benzene containing a little ligroin, then from glacial acetic acid. Yield of purified product was 23% of theory, m.p. 167–168.5°.

Anal.[34] Calcd. for $C_{13}H_8O_2Br_2Cl_2$: Br, 37.44; Cl, 16.38. Found: Br, 36.65; Cl, 15.90. Molec. Wt. (Rast in D-camphor): Calcd. 426.9; found: 427.6.

Reactions of 3,5-dibromo 2-hydroxybenzyl bromide (I) *in presence of silver perchlorate. A. Nitromethane as solvent.* Silver perchlorate (0.025 mole) and 2,6-dichlorophenol (0.075 mole) were dissolved in 30 ml. of nitromethane and a solution of 0.025 mole of I in 170 ml. of nitromethane was added dropwise. The solution became warm, turned yellow in color, and an immediate precipitate of AgBr appeared. Stirring was continued for 1 hr. after addition of benzyl bromide was complete. The precipitate was removed by filtration, washed with nitromethane, and the combined filtrates shaken with calcium carbonate (0.025 mole) to neutralize acid. Filtration followed by distillation of solvent under reduced pressure left a tan residue. This was purified by dissolving in hot benzene, decolorizing with charcoal and adding petroleum ether to the first appearance of cloudiness. Chilling overnight gave 6.6 g. (62%) of light yellow crystals, m.p. 165.5–167°. There was no depression of melting point on admixture with compound II, above.

A similar experiment in which only 0.5 g. of silver perchlorate was used as catalyst instead of an equivalent amount, as above, gave essentially no reaction. On evaporating the solvent and recrystallizing, only the starting materials were recovered.

B. Toluene as solvent. 3,5-dibromo 2-hydroxy 4'-(or 2'?)-methyldiphenylmethane. The preceding experiment was repeated but substituting a total of 180 ml. of toleune for the nitromethane as solvent. The filtration yielded 93% of the calculated amount of AgBr. The toluene solution was treated with solid calcium carbonate to remove acid and dried with anhydrous calcium sulfate. Toluene was removed under vacuum and the residue recrystallized from glacial acetic acid, then from aqueous alcohol. The melting point was 117–118°, and a mixture with the starting benzyl bromide (m.p. 118°) caused a depression of melting point. Yield of the purified material corresponded to 39% of theory based on equimolar reaction between the benzyl bromide (I) and toluene. Analyses confirmed the conclusion that the product was a diphenylmethane compound, free of chlorine, and containing two bromine atoms and one hydroxyl group per molecule. Location of the methyl group was not positively established, but the infrared absorption pattern in the 5.1–6.0 micron region, together with a strong band at 12.5 microns support the structure in which the methyl group is in the 4 position with respect to the methylene bridge.[35]

Anal.[34] Calcd. for $C_{14}H_{12}OBr_2$: C, 47.22; H, 3.40; Br, 44.77. Found: C, 47.74; H, 3.25; Br, 45.11. Hydroxyl content (acetic anhydride in pyridine): Calcd. 4.77; found 4.62% OH. Molecular weight (Rast in D-camphor): Calcd. 356.1; found 362.4.

3,5-Dibromo-3',5'-dimethyl 2,2'-dihydroxydiphenylmethane. Compound I (0.05 mole) and 2,4-dimethylphenol (0.05 mole) were heated 5 hr. at 140° in an atmosphere of nitrogen. Hydrogen bromide was evolved continuously. After cooling, the residue was recrystallized from benzene (charcoal), then from aqueous alcohol. Yield, 40% (7.6 g.) of crystals, m.p. 178.6–179.6°.

Anal.[34] Calcd. for $C_{15}H_{14}O_2Br_2$: Br, 41.40. Found: Br, 41.23.

It is here evident that the increased ability of the reaction to propagate (dependent on the relative reactivity of the addend) is important, as well as the initiation step (carbonium ion formation).

3',5',5-Tribromo 2,4'-dihydroxydiphenylmethane. In agreement with Finn and Lewis,[9] we were unable to obtain this compound from the starting materials alone or in combination with acids. However, a solution of 0.05 mole of 3,5-dibromo-4-hydroxybenzyl bromide (prepared by bromination of *p*-cresol[9]) in 300 ml. of nitromethane, added dropwise to a solution of 0.05 mole of *p*-bromophenol and 0.05 mole of silver perchlorate in 50 ml. of nitromethane gave a precipitate of silver bromide. The organic product, after removal of the nitromethane, yielded two distinct crystalline substances following separation of oily and resinous material by fractional precipitation from benzene with petroleum ether. The first crop of crystals (1.4 g.) had m.p. 195–197° which increased to 211° on further recrystallization from benzene. On the basis of its infrared spectrum indicating 1,2,3,5 aromatic substitution,[35] it appears to be 2,6-bis(3',5'-dibromo-4'-hydroxybenzyl)-4-bromophenol, a product of condensation of 4-bromophenol with two molecules of the *p*-hydroxybenzyl compound. The spectrum was also very similar to that of the corresponding trinuclear compound in which all halogens are replaced by methyl groups.

The second fraction after recrystallization from benzene-petroleum ether gave 1.6 g. of light yellow solid, m.p. 131.5–132.5°.

Anal.[34] Calcd. for $C_{13}H_9O_2Br_3$: Br, 54.9. Found: Br, 54.8.

Infrared absorption bands in the 11–12.5 micron region indicate presence of 1,2,3,5 and 1,2,4 substituion.[35]

2,2'-Dihydroxy-3,3'-dimethyl-5,5'-di-tert-butyldibenzyl ether. This compound was obtained from an experiment intended to produce the monomethylol of *p-tert*-butyl-*o*-cresol as reported by Hultzsch.[36] The procedure had been used previously by Dr. G. R. Sprengling in our laboratory to prepare the methylol compound successfully, the only change being his use of dilute acetic acid where we have used hydrochloric acid.

In our experiment, 1.5 moles (246.2 g.) of *p*-tert-butyl-*o*-cresol was dissolved in a solution of 1.5 moles (60 g.) of sodium hydroxide in 550 ml. of water by warming at 60°. After cooling to 35°, 1.7 moles (138 g.) of 37% formaldehyde solution was added. On shaking, a slight exothermic reaction raised the temperature briefly to 43°. After 24 hr. at room temperature, the solution was acidified to *p*H 5 by dilute HCl while cooling in ice. A heavy oil separated and, on standing over the week end, it solidified. After separation by filtering, the substance was ground in a mortar with 150 ml. of 1.0*N* HCl. It was again filtered and the mass dissolved in 250 ml. of ethyl ether, dried over anhydrous calcium sulfate and the ether evaporated on a water bath. The temperature did not rise above 70°. On standing in a vacuum desiccator, the residual oil again solidified.

The product was recrystallized from 150 ml. of hot hexane by chilling. After separation of the initial crop of 86 g. of crystals, the filtrate was evaporated to give a resinous oil which on long standing produced an additional crop of 36 g. of crystals plus some oil. The combined crystalline fractions represented a yield of 44% of theoretical for the dibenzyl ether. Subsequent recrystallization from hexane containing a little benzene gave white needles, m.p. 130° and producing no depression of melting point when mixed with an authentic sample of the dibenzyl ether prepared according to

(34) Analyses reported for C, H, were performed by Galbraith Laboratory, Knoxville, Tenn. Halogen determinations are by Miss M. Mistrick of this laboratory.

(35) Infrared data were provided by Dr. J. H. Lady, of this laboratory, using a Perkin-Elmer, Model 21 Spectrophotometer. Assignment of absorption bands was in accordance with L. J. Bellamy, "Infrared Spectra of Complex Molecules," J. Wiley and Sons, New York, 1956, p. 57.

(36) K. Hultzsch, *J. prakt. Chem.*, 158, 275 (1941).

Hultzsch[37] by heating the intermediate methylol compound (m.p. 64°).

Zigeuner and Ziegler[28] have likewise reported formation of the dibenzyl ether of the analogous 2,4-dimethylphenol without use of high temperatures, simply by treating the corresponding methylol compound with dilute HCl in boiling acetone–benzene mixture.

(37) K. Hultzsch, *J. prakt. Chem.*, **159**, 169 (1942).

PITTSBURGH, PA.

[CONTRIBUTION FROM BATTELLE MEMORIAL INSTITUTE]

Synthesis of Pyromellitonitrile and Related Compounds[1]

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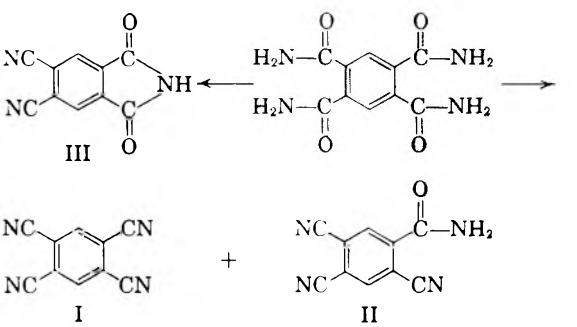
Pyromellitonitrile was prepared by the dehydration of pyromellitamide with thionyl chloride in dimethylformamide. The tetramide could not be dehydrated to the tetranitrile with acetic anhydride, phosphorus oxychloride, phosphorus pentachloride, or benzenesulfonyl chloride. By-products of the thionyl chloride dehydration were 4,5-dicyanophthalimide, and 2,4,5-tricyanobenzamide. 2,5-Dibromoterephthalic acid reacted quantitatively with cuprous cyanide to form pyromellitimide, but dimethyl 2,5-dibromoterephthalate reacted under the same conditions to form dimethyl 2,5-dicyanoterephthalate. Tetrakis(*N*-ethyl)pyromellitamide reacted with phosphorus pentachloride to form *N,N'*-diethylpyromellitimide.

During a study of the preparation of various phthalocyanines, it was necessary to prepare pyromellitonitrile (1,2,4,5-tetracyanobenzene, I) as an intermediate. The compound proved unexpectedly difficult to prepare and until a successful synthesis was achieved several new compounds were prepared, the syntheses of which we are reporting. The only reference to I in the literature was a patent[3] which stated that it was prepared "from pyromellitic acid tetramide by conventional methods"; no other description was given. Accordingly, pyromellitamide was prepared from pyromellitic acid by the method of Meyer and Steiner[4] in 88 per cent yield. However, the next step of dehydration of the tetramide to I proved unexpectedly difficult. Although good yields of *o*-phthalonitrile can be obtained by dehydration of *o*-phthalamide, using various methods, the analogous dehydrations of the tetramide to I were generally unsuccessful. For example, acetic anhydride in the presence of chlorobenzene was reported[5] to give a quantitative yield of *o*-phthalonitrile from *o*-phthalamide. An attempt to dehydrate the tetramide by a similar procedure gave only starting material. Similarly, dehydrations with phosphorus pentachloride, phosphorus oxychloride,[6] benzenesulfonyl chloride,[7] phosphorus pentoxide, and carbonyl chloride, yielded starting material, pyromellitimide, or chars.

This dehydration was finally accomplished with thionyl chloride in dimethylformamide at 60°. Stoichiometric proportions yielded a mixture of 2,4,5-tricyanobenzamide (II), pyromellitimide, and some I. Further reacting this mixture with additional thionyl chloride and recrystallizing from ethanol gave I.

When pyromellitamide reacted with an excess of thionyl chloride at a slightly higher tmeperature, the new compound 4,5-dicyanophthalimide (III) was the major product. All these *o*-dicyanobenzenes pass through a characteristic sequence of color changes from white at room temperature, slowly changing to green on heating above 200°, and abruptly turning deep blue between 255° and 260°. *o*-Phthalonitrile does likewise in a sealed capillary. This apparently is a characteristic of the *o*-dinitrile grouping.



Pyromellitamide is high melting and very insoluble in common solvents, due to strong hydrogen bonding in this planar molecule. With the objective of reducing the hydrogen bonding, leaving the molecule more susceptible to attack by dehydrating agents, both tetrakis(*N,N*-diethyl)pyromellitamide (IV) and tetrakis(*N*-ethyl)pyromel-

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(2) Present address: Rocketdyne, 6633 Canoga Avenue, Canoga Park, Calif.

(3) Farbenfabriken Bayer, Brit. Patent 698,049 (1953).

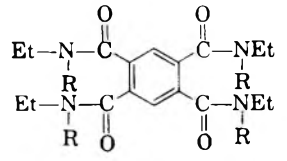
(4) H. Meyer and K. Steiner, *Monatsch.*, **35**, 39 (1914).

(5) E. Koike, M. Okawa, and K. Uchiyama, *J. Chem. Soc., Japan, Ind. Chem. Sect.* **57**, 925 (1954); *Chem. Abstr.*, **50**, 884*g* (1956).

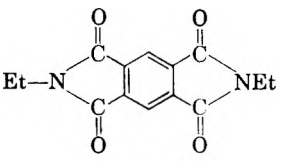
(6) M. H. Fleysher, U. S. Patent 2,387,435 (1945).

(7) C. R. Stephens, F. J. Bianco, and F. J. Pilgrim, *J. Am. Chem. Soc.*, **77**, 1701 [1955).

litamide (V) were prepared from pyromellitoyl chloride and diethylamine and ethylamine respectively. Compound V reacted smoothly with phosphorus pentachloride in carbon tetrachloride to give the new compound *N,N'*-diethylpyromellitimide (VI), m.p. 273–274°. Compound IV, however, did not react with phosphorus pentachloride under the same conditions, and tars were formed when the reaction was carried out in higher boiling solvents.

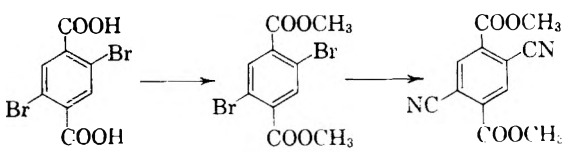


IV. R = Et
V. R = H



VI

Since four amide groups seemed so difficult to dehydrate simultaneously, it was thought that two para amide groups would dehydrate more readily. Accordingly, *p*-xylene was brominated to yield, 2,5-dibromo-*p*-xylene,[8] which in two steps was converted to 2,5-dibromoterephthalic acid (VII).[9] VII was esterified and the dimethyl 2,5-dibromoterephthalate (VIII) converted to dimethyl 2,5-dicyanoterephthalate (IX) using a variation of the Rosenmund-Von Braun substitution.[10] On recrystallization from ethanol, two fractions were obtained. One fraction melting at 219° was identified by elemental and spectral analysis as the expected dimethyl 2,5-dicyanoterephthalate. A second fraction melting at 195–198° was less pure and contained another compound, possibly 4-cyano-5-carbomethoxyphthalimide as evidenced by mixed melting point and infrared spectra. It was planned to convert IX to the dicyano diamide which might subsequently be dehydrated to I, but upon the successful dehydration of pyromellitamide this approach was abandoned.



VII VIII IX

In an attempt to prepare 2,5-dicyanoterephthalic acid directly from VII before esterification, a quantitative yield of pyromellitimide was obtained. Apparently the desired 2,5-dicyanoterephthalic acid underwent rearrangement to the diimide. Scholl and Neuberger[11] reported that the analogous rearrangement of *o*-cyanobenzoic acid to phthalimide occurs on heating to 180°, and at 60° in the presence of thionyl chloride. The tendency for this rearrangement to occur in the presence of a Lewis acid such as thionyl chloride may explain in part the conversion of pyromellitamide to pyromellitimide by phosphorus pentachloride and other dehydrating agents, and also the presence of 4,5-dicyanophthalimide as a product of the reaction of pyromellitamide with a large excess of thionyl chloride.

(8) R. Fittig, W. Ahrens, L. Mattheides, *Ann.*, **147**, 26 (1868).

(9) B. Schultz, *Ber.*, **18**, 1762 (1885).

(10) Lester Friedman, private communication.

(11) R. Scholl and W. Neuberger, *Monatsh.*, **33**, 517 (1912).

EXPERIMENTAL

All melting points were determined in capillary tubes and are corrected.

Pyromellitonitrile (I). A stirred suspension of pyromellitamide (10 g., 0.04 mole) in dimethylformamide (56 g.) was warmed to 60° before thionyl chloride (19.2 g., 0.16 mole) was added dropwise. After the mixture was heated for 7 hr. at 60°, dilute hydrochloric acid was added to decompose unreacted thionyl chloride, and the mixture was filtered. The residue was washed with water until it was neutral to litmus and then was slurried four times in hot, glacial acetic acid and filtered hot. The insoluble fraction was crude pyromellitimide, m.p. 450–454° dec. (lit. value[3] 440°). The products recovered from the acid extract, when added to a boiling solution of sodium isoamyloxide in isoamyl alcohol, gave an immediate blue color of phthalocyanine, indicating the presence of ortho nitrile groups.[12] The infrared spectrum showed a strong CN absorption at 4.5 μ and weaker NH and CO bands at 3.2 and 5.8μ, respectively. The flat platelets exhibited the unusual melting point characterisics attributed to *o*-dicyanobenzenes. Elemental analysis indicated the material to be essentially II.

Anal. Calcd. for $C_{10}H_4N_4O$: C, 61.2; H, 2.0; N, 28.6. Found: C, 63.5; H, 1.2; N, 28.9.

Five grams of the crude product were dissolved in dimethylformamide and 12 ml. (0.16 mole) of thionyl chloride were added. The solution was heated for 2 hr. with stirring. The reaction mixture was poured slowly onto crushed ice, and the white precipitate was extracted with glacial acetic acid as before. A light tan powder recovered from the acetic acid solution was crystallized in fine needles from boiling ethanol to yield 2.0 g. of I, m.p. 258° (sealed tube), turning blue. The infrared spectrum (KBr pellet) had bands at 4.5μ (CN), 3.2μ, 3.3μ (CH), and 10.8μ (1,2,4,5-substitution). It gave a positive sodium isoamyloxide test for ortho nitrile groups.

Anal. Calcd. for $C_{10}H_2N_4$: C, 67.3; H, 1.1; N, 31.4. Found: C, 67.0; H, 1.5; N, 31.2.

4,5-Dicyanophthalimide (III). Pyromellitamide and thionyl chloride in a ratio of 1:16 were dissolved in dimethylformamide and heated for 1 hr. on a steam bath at 98°. The cooled reaction mixture yielded a yellow precipitate when poured into a slurry of crushed ice and hydrochloric acid. The precipitate was filtered, washed with water until the washings were neutral, and extracted twice with hot glacial acetic acid. The residue was pyromellitimide; addition of water to the extract precipitated a brown powder m.p. 275–280° dec. which gave a negative sodium isoamyloxide test and was not characterized. Ether extraction of the aqueous acetic acid solution yielded a yellow powder, which turned blue at 260° and which was shown to contain ortho nitrile groups by the sodium isoamyloxide test. Infrared absorption bands at 4.5μ (CN), 3.2μ (NH), and 5.7–5.9μ (CO) indicated that the compound was 4,5-dicyanophthalimide.

Anal. Calcd. for $C_{10}H_3N_3O_2$: N, 21.3. Found: N, 21.0.

Tetrakis(N-Ethyl)Pyromellitamide (V). Compound V was prepared by dropping an ether solution of ethylamine into

(12) Ciba Brit. Patent 698,048, April 28, 1954; *Chem. Abstr.*, **48**, 11803 (1954).

a stirred, ice-cooled, ether solution of pyromellitoyl chloride until the solution was basic. The precipitates were filtered from the ether and excess amine and were water washed until the washings were chloride free. The product was insoluble in cold but soluble in hot ethanol and methanol. It was insoluble in ether, ligroin, benzene, nitrobenzene, and chloroform. Recrystallization from ethanol yielded pure white needles of V, m.p. 280–281°.

Anal. Calcd. for $C_{18}H_{26}N_4O_4$: N, 15.4. Found: N, 15.1.

Tetrakis(N,N-diethyl)pyromellitamide (IV). Compound IV was prepared by dropping an ether solution of diethylamine into a stirred, ice-cooled, ether solution of pyromellitoyl chloride until the solution was basic. The precipitates were filtered from the ether and excess amine and were water washed until the washings were chloride free. The product was very soluble in ethanol, methanol, glacial acetic acid, and hot carbon tetrachloride. It was recrystallized from chloroform by adding ether with strong cooling to give pure white needles of IV, m.p. 190–192°.

Anal. Calcd. for $C_{26}H_{46}O_4N_4$: N, 11.7. Found: N, 11.3.

N,N'-Diethyl pyromellitimide (VI). In a three-necked flask equipped with a thermometer, stirrer, and reflux condenser were placed IV (5.0 g., 0.014 mole), phosphorus pentachloride (12.5 g., 0.06 mole), and chloroform (250 ml.). The mixture was heated slowly to reflux and maintained there for 6 hr. The cooled chloroform solution was poured into crushed ice, and the chloroform layer was separated, filtered, and washed alternately with aqueous sodium bicarbonate followed by water until the washings were no longer acid. Evaporation of the solvent left a yellow-brown powder, 3.2 g., m.p. 270–273°. The product was soluble cold in chloroform, benzene, dioxane, and glacial acetic acid and soluble hot in carbon tetrachloride, ethanol, and methanol. It was insoluble in ligroin and ether. Recrystallization from ethanol yielded 2.3 g. (61%) of VI, m.p. 273–274°.

Anal. Calcd. for $C_{14}H_{12}N_2O_4$: C, 61.8; H, 4.4; N, 10.3. Found: C, 61.6; H, 4.2; N, 10.3.

The Friedman modification of the Rosenmund-Von Braun reaction. In a 50 ml. resin kettle were placed 2,5-dibromoterephthalic acid (2.0 g., 0.0062 mole), cuprous cyanide (1.4 g., 0.015 mole), and dimethylformamide (3 ml.). The mixture was heated slowly with stirring to reflux and after an hour was poured into a solution of ferric chloride (3.0 g.), concd. hydrochloric acid (1.0 ml.) and water (4.0 ml.). The mixture was heated to 60° for 10 min. to decompose the complex, cooled, and filtered. The product was insoluble in glacial acetic acid and was recrystallized from dimethylformamide to yield pyromellitimide (1.3 g., 98%) as shown by melting point and comparison of its infrared spectrum with that of an authentic sample.

Dimethyl-2,5-dibromoterephthalate (VIII). Anhydrous hydrogen chloride was passed into a flask containing 2,5-dibromoterephthalic acid (7.0 g., 0.216 mole) dissolved in absolute methanol (80.0 ml.) until the solution was nearly saturated. After refluxing for 8 hr., the solution was cooled to room temperature to precipitate white crystalline platelets of VIII, m.p. 148.6° (7.2 g., 97%).

Anal. Calcd. for $C_{10}H_8Br_2O_4$: C, 33.6; H, 2.3. Found: C, 34.2; H, 2.3.

Dimethyl-2,5-dicyanoterephthalate (IX). The Friedman modification[9] of the Rosenmund-Von Braun reaction was repeated on 2.0 g. of VIII. The pink filter cake obtained from the ferric chloride solution weighed 1.3 g. (m.p. 197–200°). Recrystallization from ethanol gave 0.4 g. of VIII, m.p. 219°. Infrared absorption showed the presence of CN (4.5μ), and CO plus CH_3OCO (5.8–5.9μ, 7.8–8.1μ, and 8.8μ). There were no bands characteristic of NH.

Anal. Calcd. for $C_{12}H_8N_2O_4$: N, 11.5. Found: N, 11.3.

Another fraction from the ethanol mother liquid melted at 195–198°. A mixed melting point with dimethyl-2,5-dicyanoterephthalate was 205–212°. The intermediate temperature but wider range makes it appear that this second fraction was another compound. Its infrared spectrum showed the presence of NH but was otherwise quite similar to that of the first fraction. It is possible that this material was a mixture of some dimethyl-2,5-dicyanoterephthalate with a substantial amount of 4-cyano-5-carbomethoxyphthalimide. Neither fraction contained halogen. The identity of the second fraction was not established.

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COLUMBUS, OHIO

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CINCINNATI]

Substituted γ-Lactones. I. Preparation of α-Substituted γ-Butyrolactones by Condensation of γ-Butyrolactone with Aldehydes. Hydrogenation of the Condensation Products

HANS ZIMMER AND JOHANNES ROTHE[1]

Received June 30, 1958

The base-catalyzed condensation of γ-butyrolactone with various aldehydes is described. These condensation products can be hydrogenated to the corresponding saturated α-substituted γ-butyrolactones.

The γ-lactone ring occurs in a large variety of natural products, many of which exhibit considerable pharmacological interest.[2] As examples, the digitalis-glycosides, santonin, lignans like podophyllotoxin, and antibiotic substances like patulin may be cited. Among the more recent findings, only the antibiotic PA-147[3] and acetomycin[4] shall be mentioned.

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(2) *Cf.* L. J. Haynes, *Quart. Rev.*, **2**, 46 (1948).

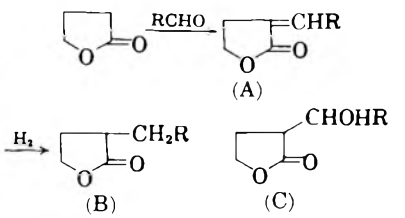
(3) H. Els, B. A. Sobin, and W. D. Celmer, *J. Am. Chem. Soc.*, **80**, 878 (1958).

(4) L. Ettlinger, E. Gäumann, R. Hütter, W. Keller-Schierlein, F. Kradolfer, L. Neipp, V. Prelog, and H. Zahner, *Helv. Chim. Acta*, **41**, 216 (1958).

We were interested in preparing certain α- and/or β-substituted butyrolactones in order to investigate some of their physiological activities. Some of the compounds were also wanted as model compounds or as intermediates in further synthetic work in the γ-lactone field. In this paper the preparation of a number of α-substituted products is described.

Various methods are described in the literature for the preparation of α-substituted lactones containing neither β- nor γ-substituents. Besides lactonization of appropriate γ-hydroxy- or γ-halo acids, the most versatile approach seems to be the condensation of malonic[5] or acetoacetic esters[6] with ethylene oxide or ethylene chlorohydrin followed by hydrolysis and decarboxylation or ketonic cleavage, respectively.

Another method which was adopted in the present investigation is the condensation of butyrolactone with carbonyl compounds, especially with aldehydes. Reactions of this kind have been performed[7] with unsaturated lactones of the type of Δ^2-angelicalactone; the condensation proceeds smoothly by heating the reactants with a catalytic amount of an organic base like diethylamine. γ-Valerolactone was the first saturated lactone which was condensed with benzaldehyde, piperonal and heptaldehyde by Losanitsch.[8] α-Benzalbutyrolactone (A, R = C_6H_5) was prepared by Pinder[9] and by Reppe[10] who also condensed butyrolactone with *o*-chlorobenzaldehyde, furfural, nonaldehyde, and cyclohexanone and obtained the corresponding saturated compounds (B) by hydrogenation.



With saturated lactones, stronger bases must be employed as condensing agents. We adopted the method of Reppe[10] (sodium methoxide in benzene at room temperature) and extended it to a number of other aldehydes, mostly aromatic ones; isovaleraldehyde was the only aliphatic representative being included in our investigation. The inexpensive lactone was always applied in excess. Generally the reaction gives reasonable yields; sometimes, it was found advantageous to heat the reaction mixture. In one case (R = *o*-ethoxyphenyl), a small amount of a compound was isolated which is believed to be the primary product C of the aldolic condensation.

We were not interested in elaborating the optimal conditions in every single case. With several aldehydes, only one experiment was run; thus, some of the yields given might not represent the maximal ones obtainable. Nevertheless, a certain trend in the yields is evident which apparently is dependent on the electronegative character of the aldehydes. The condensation did not proceed well with negatively substituted benzaldehydes (*o*-, *m*-, *p*-nitro-, *p*-cyano-, *p*-acetamido) and with pyridine carboxaldehydes. Low yields were obtained together with tars and unidentified noncrystalline side-products. Assuming the mechanism of the common aldol condensation, these findings are rather unexpected.[11] One should expect that the electron-withdrawing effect of the negative substituent makes the carbonyl carbon of the aldehyde particularly susceptible to condensation with the anionoid α-position of the butyrolactone. This influence on the yields has been clearly observed in related reactions of the aldol type; *e.g.*, in the Perkin reaction,[12] the nitrobenzaldehydes give yields from 75 to 82% of the corresponding cinnamic acids while the unsubstituted benzaldehyde furnishes only 45–50%. Parallel to our findings, however, is the behavior of the nitrobenzaldehydes in the Stobbe condensation[13] with diethyl succinate; under the classical conditions[14] (sodium ethoxide in ether in the cold, thus similar to the conditions in the present investigation) only resinous products were obtained.

Assuming that the higher reactivity of the nitrobenzaldehydes might have led to excessive secondary reactions, we attempted to counteract this reactivity to get better results by use of short reaction periods and low temperatures. However, the results remained the same.

On the other hand, compounds with electron-releasing substituents such as *p*-dimethylaminobenzaldehyde gave fairly good yields. This aldehyde fails completely in the Perkin reaction. Alkyl- and alkoxybenzaldehydes which give low yields in the Perkin reaction worked well in our condensation experiments. At present we do not have any reasonable explanation for these findings. However, several authors report that in certain aldol-type condensations of aldehydes with compounds con-

(5) *e.g.*, R. Fittig, *Ann.*, **226**, 322 (1884); I. L. Knunyantz, G. W. Chelintzev, and E. D. Osetrova, *Chem. Abstr.*, **28**, 4383² (1934).

(6) *e.g.*, W. Traube and E. Lehmann, *Ber.*, **34**, 1971 (1901); B. Rothstein, *Bull. soc. chim. France*, (5) **2**, 80 (1935); K. Wiesner, Z. Valenta, A. J. Manson, and F. W. Stonner, *J. Am. Chem. Soc.*, **77**, 675 (1955).

(7) *e.g.*, J. Thiele and F. Straus, *Ann.*, **319**, 155 (1901); J. Thiele, R. Tischbein, and E. Lossow, *Ann.*, **319**, 180 (1901); W. F. v. Oettingen, *J. Am. Chem. Soc.*, **52**, 2024 (1930); D. H. Marrian, P. B. Russell, and A. R. Todd, *Biochem. J.*, **45**, 533 (1949).

(8) M. S. Losanitsch, *Monatsh.*, **35**, 311 (1914).

(9) A. R. Pinder, *J. Chem. Soc.*, 2236 (1952).

(10) W. Reppe *et al.*, *Ann.*, **596**, 158 (1955).

(11) E. R. Alexander, *Principles of Ionic Organic Reactions*, John Wiley & Sons, Inc., New York, 1950, p. 176.

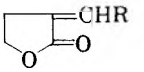
(12) J. R. Johnson, *Org. Reactions*, **1**, 210 (1942).

(13) W. S. Johnson and G. H. Daub, *Org. Reactions*, **6**, 1 (1951).

(14) H. Stobbe, *Ann.*, **380**, 49 (1911).

TABLE I

CONDENSATION PRODUCTS OF γ-BUTYROLACTONE WITH VARIOUS ALDEHYDES



No.	R	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	M.P., °C.	[a]	Reaction Time, Hr. Cold	Reaction Time, Hr. Heating	Yields b	Yields c
I	Isobutyl	$C_9H_{12}O_3$	70.10	70.22	9.15	9.21	[d]	...	2	0.5	78	..[e]
II	4-Methylphenyl	$C_{12}H_{12}O_2$	76.57	76.56	6.43	6.43	63 - 64	Et	3	..	46	..
III	4-Isopropylphenyl	$C_{14}H_{16}O_2$	77.74	76.63	7.46	7.67	65 - 66	Et-P	4.5	..	62	..
IV	2-Hydroxyphenyl	$C_{11}H_{10}O_3$	69.46	69.44	5.30	5.51	184 -185	M	3	0.75	63	93[f]
V	3-Hydroxyphenyl	$C_{11}H_{10}O_3$	69.46	69.55	5.30	5.33	196 -197	M	4.5	1	69	..[g]
VI	4-Hydroxyphenyl	$C_{11}H_{10}O_3$	69.46	69.05	5.30	5.38	181 -182	W	15	1	44	70[h]
VII	4-Methoxyphenyl	$C_{12}H_{12}O_3$	70.57	70.35	5.92	5.95	126 -127	E	2	1	48	..[c]
VIII	2-Ethoxyphenyl	$C_{13}H_{14}O_3$	71.54	71.45	6.47	6.45	105 -105.5	M	2.5	..	79	..[i]
IX	3,4-Dimethoxyphenyl	$C_{13}H_{14}O_4$	66.66	66.81	6.02	6.16	116 -116.5	M	Short	0.5	53	..
X	3,4-Diethoxyphenyl	$C_{15}H_{18}O_4$	68.68	68.85	6.92	6.92	116	M	4.5	0.5	63	..
XI	3,4,5-Trimethoxyphenyl	$C_{14}H_{16}O_5$	63.63	63.59	6.10	6.10	152 -152.5	M	1	0.5	58	..[e]
XII	3,4-Methylenedioxyphenyl	$C_{12}H_{10}O_4$	66.05	65.90	4.62	4.64	178 -178.5	D	3.5	..	82	..
XIII	4-Benzyloxyphenyl	$C_{18}H_{16}O_3$	77.12	76.60	5.75	6.04	166 -166.5	A	1	0.5	71	..
XIV	3-Methoxy-4-benzyloxyphenyl	$C_{19}H_{18}O_4$	73.53	73.23	5.85	5.98	151 -152	D	1.5	1	74	..
XV	4-Isopropoxyphenyl	$C_{14}H_{14}O_3$	72.39	72.26	6.94	7.05	115 -115.5	M	1	2.5	79	98
XVI	4-(2-Butoxy)-phenyl	$C_{15}H_{16}O_3$	73.75	73.42	6.60	7.40	54 - 55.5	M	2	0.5	24	..[e,j]
XVII	3-Methoxy-4-hydroxyphenyl	$C_{12}H_{12}O_4$	65.45	65.20	5.49	5.45	153.5-154	W	4	1	6	..[k]
XVIII	4-Chlorophenyl	$C_{11}H_9ClO_2$	63.32	63.46	4.35	4.50	142 -144	E	2	..	79	..
XIX	3-Nitrophenyl	$C_{11}H_9NO_4$	60.27	60.70	4.14	4.23	147 -148	M	1	1	15	..[l]
XX	4-Nitrophenyl	$C_{11}H_9NO_4$	60.27	60.17	4.14	4.22	202 -203	Mc	1	1	1	..[m]
XXI	4-Dimethylaminophenyl	$C_{13}H_{15}NO_2$	...	...	..	..	195 -196	D	1	0.5	59	87[n]
XXII	4-Diethylaminophenyl	$C_{15}H_{19}NO_2$	...	...	..	..	126 -128	E	2	0.5	56	..[o]
XXIII	4-Acetamidophenyl	$C_{13}H_{13}NO_3$	...	...	..	..	199 -200	M	Short	1	2	..[p]
XXIV	Phenylvinyl	$C_{13}H_{12}O_2$	77.98	77.73	6.04	6.26	133.5-135	M	0.5	..	67	..
XXV	*p*-Dimethylaminophenylvinyl	$C_{15}H_{17}NO_2$	...	...	..	..	181 -182	D	2	..	54	..[e,q]
XXVI	1-Naphthyl	$C_{15}H_{12}O_2$	80.33	80.25	5.39	5.50	104 -105	M	1	..	23	..
XVII	2-Furylvinyl	$C_{11}H_{10}O_3$	60.46	69.33	5.30	5.36	98 - 99	E	1	1	62	..

The following compounds are colored: XIII, XIV, XIX, XX, XXIV, yellowish; XXVII, brownish; XXII, yellow; XXI, yellow-greenish; XXV, orange-red. The following give a coloration with $FeCl_3$ in dioxane or ethanol: IV, yellowish green; VI and XVII, green. The following give a coloration with H_2SO_4 in the cold: IV, V, VII–XI, yellow; XIII, XXV, orange; VI, XIV, red; XXVII, brown; XXVI, yellowish brown; XII, brownish. [a] Solvents for recrystallization: E = Ethyl alcohol, Et = diethyl ether, P = petroleum ether b.p. 40–60°, M = methanol, W = water, D = dioxane, A = acetic acid, Mc = methylene chloride. [b] Based on applied aldehyde. [c] Based on consumed aldehyde. [d] B.p. 99–100°/3 mm; n_D^{20} 1.4751. [e] Only one experiment; yield can possibly be improved. [f] *Acetyl deriv.*, m.p. 122–123° (from methanol). *Anal.*: Calcd. for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21. Found: C, 66.84; H, 5.34. [g] *Acetyl deriv.*, m.p. 108.5–110° (from methanol). *Anal.*: Found: C, 67.08; H, 5.41. [h] *Acetyl deriv.*, m.p. 142.5–143.5° (from benzene). Anal.: Found: C, 67.13; H, 5.25. [i] In this experiment, a 5% yield of a *compound* $C_{13}H_{16}O_4$, m.p. 134.5–136° (from methanol) was isolated from the sulfuric acid layer; the properties of this substance (Calcd.: C, 66.13; H, 6.83. Found: C, 65.93; H, 6.96. Infrared spectrum in nujol: bands at 2.93 [OH] and 5.68μ [lactone], no band between 6.0 and 6.2μ. Insoluble in cold dilute sodium carbonate solution) correspond best to the primary aldolic product (C, R = *o*-ethoxyphenyl). The compound was not investigated further. [j] Low yield probably due to small amount of starting material. [k] *Acetyl deriv.*, m.p. 151.5–152.5° (from methanol). Anal.: Calcd. for $C_{14}H_{14}O_5$: C, 64.11; H, 5.38. Found: C, 64.11; H, 5.39. [l] Calcd.: N, 6.39. Found: N, 6.45. [m] Calcd.: H, 6.39. Found: N, 6.32. [n] Calcd.: N, 6.45. Found: N, 6.33. *Hydrochloride*, m.p. 178° (dec.; from methanolic HCl), is white, but turns yellow-greenish in the open air or in a desiccator ($CaCl_2$); stable in HCl-atmosphere; not analyzed. [o] Calcd.: N, 5.71. Found: N, 5.61. *Hydrochloride*, m.p. 203–204° (dec.; from 7% aq. HCl), White, not quite as unstable as the preceding hydrochloride. Anal.: Calcd. for $C_{15}H_{20}ClNO_2$: Cl, 12.58. Found: Cl, 12.72. [q] Calcd.: N, 5.76. Found: N, 5.82.

taining active methyl groups (substituted toluenes,[15] picoline methiodide[16]), *p*-dimethylaminobenzaldehyde gives better results than the unsubstituted benzaldehyde. A mechanism proposed for the latter reaction[16] seems not to be applicable in the present case.

In spite of several attempts, and unexpectedly after the good yields with other hydroxy or methoxy substituted aldehydes, the condensation did not proceed well with vanillin. Haworth[17] reported a failure in an attempted Stobbe condensation with this compound and circumvented the difficulties by application of benzylvanillin. We did likewise

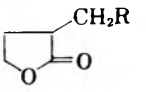
(15) L. Chardonnens and W. J. Kramer, *J. Am. Chem. Soc.*, **79**, 4955 (1957).

(16) A. P. Phillips, *J. Org. Chem.*, **12**, 337 (1947).

(17) R. D. Haworth and F. H. Slinger, *J. Chem. Soc.*, 1098 (1940).

TABLE II

HYDROGENATION PRODUCTS



R	Formula	Analytical Values C Calcd.	C Found	H Calcd.	H Found	M.P. or B.P., °C.	Solvent for Recrystallization or n_D^{20}	Yield
4-Methylphenyl	$C_{12}H_{14}O_2$	75.75	75.83	7.43	7.89	135/4 mm.	1.5272	99
4-Isopropylphenyl	$C_{14}H_{18}O_2$	77.03	76.69	8.31	8.48	138–140/5 mm.	1.5219	92
2-Hydroxyphenyl	$C_{11}H_{12}O_3$	68.73	68.12	6.29	6.20	174–175/5 mm.	1.5485	76
3-Hydroxyphenyl	$C_{11}H_{12}O_3$	68.73	68.74	6.29	6.51	120–121	W-M[a]	85[a]
4-Hydroxyphenyl	$C_{11}H_{12}O_3$	68.73	68.04	6.29	6.26	192–193/4 mm.	1.5546	83
4-Methoxyphenyl	$C_{12}H_{14}O_3$	69.88	69.98	6.84	6.86	44	Et-P	76
2-Ethoxyphenyl	$C_{13}H_{16}O_3$	70.88	70.86	7.32	7.43	154–156/5 mm.	1.5421	95[a]
3,4-Dimethoxyphenyl	$C_{13}H_{16}O_4$	66.08	66.13	6.83	6.94	105.5–106.5	M	81
3,4-Diethoxyphenyl	$C_{15}H_{20}O_4$	68.16	68.31	7.63	7.66	68–69	M	80
3,4,5-Trimethoxyphenyl	$C_{14}H_{18}O_5$	63.14	62.86	6.82	6.97	72	M	83
3,4-Methylenedioxyphenyl	$C_{12}H_{12}O_4$	65.44	65.25	5.49	5.50	52–52.5	M	83
3-Methoxy-4-benzyloxyphenyl	$C_{19}H_{20}O_4$	73.06	72.12	6.45	6.52	232/4 mm.	1.5819	60[b,c]
3-Methoxy-4-hydroxyphenyl	$C_{12}H_{14}O_4$	64.85	64.62	6.35	6.43	183–184/4 mm.	1.5515	78
p-Chlorophenyl	$C_{11}H_{11}ClO_2$	62.71	62.97	5.26	5.30	159–161/4 mm.	1.5471	69
p-Dimethylaminophenyl	$C_{13}H_{17}NO_2$	71.20	71.08	7.81	7.72	92	M	95[c]
p-Diethylaminophenyl	$C_{15}H_{21}NO_2$	...	...	...	...	173–174/4 mm.	1.5534	52[c,d]
2-Phenylethyl	$C_{13}H_{16}O_2$	76.44	76.15	7.90	8.04	145–146/4 mm.	1.5224	91
2-(*p*-Dimethylaminophenyl)-ethyl	$C_{15}H_{21}NO_2$	...	...	...	...	187/4 mm.		81[e]
1-Naphthyl	$C_{15}H_{14}O_2$	79.62	78.99	6.24	6.80	205–207/6 mm.	1.5838	90
2-Furylethyl	$C_{11}H_{14}O_3$	66.64	66.35	9.15	8.98	150–152/5 mm.	1.4797	89
Isobutyl	$C_9H_{14}O_3$	...	...	...	...	83–84/5 mm.	1.4477	69[f]
p-Isopropoxyphenyl	$C_{14}H_{18}O_3$	71.77	71.66	7.74	8.68	136–141/4 mm.	1.4957	80

[a] W = water; M = methanol; Et = ether; P = petrol ether. [b] The analytical values seem to indicate that during the hydrogenation (neutral medium) the benzyl group is split off partly. This is confirmed by a weak $FeCl_3$-reaction (green) of the distilled product. [c] Hydrogenation was performed in tetrahydrofuran. [d] Calcd.: N, 5.66. Found: N, 5.34. [e] Calcd.: N, 5.66. Found: N, 5.68. The product solidified after three distillations (m.p. 34–38.5°); no attempt of recrystallization was made. [f] B. Rothstein, *Bull. soc. chim. France*, *5*, 2, (1935), gives b.p. 129°/15 mm.; n_D^{21} 1.4455.

and obtained an excellent yield of α-[3-methoxy-4-hydroxybenzylidene]-γ-butyrolactone (XVII) by hydrolyzing the benzylvanillin condensation product. (XIV). In an analogous manner, α-[*p*-hydroxybenzylidene]-γ-butyrolactone (VII) was produced from its benzyl ether (XIII).

The hydrogenation of the α-exo double bond proceeded readily at room temperature with platinum oxide under 50 lb in the Parr-apparatus. Reppe[10] had used Raney nickel under high pressure (200 atm.) at 100°.

Some of the pharmacological properties of the compounds prepared are to be reported elsewhere.

EXPERIMENTAL

Melting points are uncorrected. Microanalyses by A. Bernhardt, Mikroanalytisches Laboratorium im Max-Planck-Institut, Mülheim/Ruhr, Germany.

Materials. Generally, Eastman White Label products or comparable grades were employed without further purification.

Benzene was U.S.P. grade and was not specially dried before use. In a number of experiments, recovered benzene, dried over calcium chloride, was used, apparently without any decrease of the yields.

Sodium methoxide, from Matheson Coleman and Bell or Harshaw Chemical Co. was used. It was found that the quality of the sodium methoxide is a very decisive factor in the success of the condensations. The use of aged material that might have been partially contaminated by moisture resulted in markedly lowered yields; sometimes the reaction failed completely when sodium methoxide of a low quality was applied.

The following compounds were prepared according to standard procedures given in the literature: *Benzylvanillin*,[18] m.p. 64°. *p-Benzyloxybenzaldehyde*, m.p. 68–71°. *p-Isopropoxybenzaldehyde*,[19] b.p.$_{18}$ 120°. *p-2-Butoxybenzaldehyde*,[19] b.p.$_{19}$ 153–155°. *p*-Cyanobenzaldehyde,[20] m.p. 100°.

Condensations. (Table I). The condensations were generally run as follows: The aldehyde (0.1 mole) and 0.2 mole of butyrolactone were dissolved in 50–200 cc. of benzene. Sodium methoxide (0.15 mole) was gradually added and the mixture was continuously stirred for the periods given in Table I; for hydroxyaldehydes, 0.25 mole of CH_3ONa were used. In most cases, initial cooling (ice salt) was applied. The reactions with the more sensitive aldehydes were carried out under a stream of dry nitrogen. In a number of experiments, the mixture eventually was heated on a water bath.

The reaction mixtures were then decomposed with 10% sulfuric acid, and stirring continued for about 1 hr. to effect relactonization. In several instances, the products precipitated and could be filtered off. The filtrate was separated and the layer was discarded except in the cases of basic compounds. The benzene layer was washed with dilute

(18) R. Dickinson, I. M. Heilbron, and F. Irving, *J. Chem. Soc.*, 1888 (1927).

(19) M. Zimmer, unpublished experiments.

(20) L. Weisler, *Org. Syntheses*, Coll. Vol. II, 443 (1943).

sodium bicarbonate solution, then with water, and the benzene distilled off without previous drying (the small amount of water still being present distils azeotropically with the benzene). The residue was recrystallized or distilled, respectively, as indicated in Table I.

Example: *α-[o-hydroxybenzylidene]-γ-butyrolactone* (IV). The apparatus consisted of a 500-cc. three-neck flask fitted with a stirrer, a reflux condenser, a thermometer, and a nitrogen-inlet tube. 12.2 g (0.1 mole) of salicylaldehyde and 17.2 g. (0.2 moles) of butyrolactone were dissolved in 100 cc. of benzene. The mixture was cooled down to +3° by means of an ice salt bath. During the whole reaction the mixture was well stirred. A slow stream of nitrogen was passed over the mixture. Within 15 min., 13.5 g. (0.25 mole) of sodium methoxide were added in portions. The temperature rose to 27° and the mixture turned to a brownish jelly which was then diluted with 100 cc. of benzene. Stirring was continued for 3 more hr., then the mixture was heated on a water bath for 45 min. (temperature 60–65°).

After standing over night, sufficient 10% sulfuric acid was added under stirring to make the mixture acidic; stirring was continued for 1 hr. and the precipitate which had been formed was filtered by suction and washed thoroughly with water. Yield: 12.0 g. (63%), m.p. 184–185°. The analytical sample, after 3 recrystallizations from methanol, had the same melting point.

The filtrate was separated, the benzene layer was washed with dilute sodium bicarbonate solution, then with water and distilled. A brown oil remained which furnished, on distillation, 4.0 g. of salicylaldehyde, b.p. 195–200°. Yield based upon consumed aldehyde: 93%.

Tetrabromide of XXIV. 2 g. of XXIV were dissolved in 10 cc. of chloroform. By means of a buret, a solution of 6.2 g. bromine in 20 cc. of chloroform was added dropwise and the solution left over night in an open porcelain dish. White crystals (5.0 g., 96%), m.p. 182–183.5°, were formed after evaporation of the solvent. After 3 recrystallizations from methanol, the m.p. was 192.5–193° (dec.).

Anal. Calcd. for $C_{13}H_{12}Br_4O_2$: Br, 61.49. Found: Br, 61.86.

An attempt to prepare a bromide of XXVII by similar means resulted only in dark viscous oils.

α-[3-Methoxy-4-hydroxybenzylidene]-γ-butyrolactone (XVII) *from* XIV. 15.5 g. of XIV, 100 cc. of coned. hydrochloric acid, and 250 cc. of glacial acetic acid were heated under reflux for 1.5 hr. After standing over night the solvents were distilled off. The residue solidified and was recrystallized by dissolving in 100 cc. of methanol and adding 100 cc. of water. Yield 10.5 g. (95%), m.p. 151–152°.

α-[p-Hydroxybenzylidene]-γ-butyrolactone (VI) *from* XIII. 38.1 g. of XIII, 266 cc. of coned. hydrochloric acid, and 762 cc. of glacial acetic acid were boiled for 1.5 hr., then the solvents were removed. The residue was recrystallized from 1.5 liter of water furnishing 16.2 g. of product, m.p. 179–180°. By concentrating the mother liquors, an additional 1.5 g. (m.p. 173–176°) were obtained. Total yield: 17.7 g. (69%).

Hydrogenations (Table II). The hydrogenations were performed by dissolving or suspending 2–20 g. (mostly 5 g.) of the condensation products in 250 cc. of methanol (or tetrahydrofuran), adding 5–10% by weight of platinum oxide (by American Platinum Works) and shaking under 45–50 lbs. of hydrogen in a Parr apparatus until the pressure remained constant. Application of heat apparently had no influence on the yields. After 15 min. to 24 hr. (depending on the amount of starting material rather than on the particular compound), the pressure remained constant.

The catalyst was removed by filtration, the solvent distilled off and the residue worked up by crystallization or distillation.

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CINCINNATI 21, OHIO

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF WAYNE STATE UNIVERSITY]

The Halodiphenacyls. III. The Structure and Reactions of the Hydrogen Bromide Adduct[1]

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The adduct formed from the reaction of β-bromodiphenacyl with hydrogen bromide was shown to be the α-hydroxy-β-bromoketone III and is interpreted in this work to involve *cis* addition to the epoxide. The reaction of III with sodium iodide gave the α-hydroxy-β-methylene ketone IV, which was stable in neutral solution but which rearranged to the diketone VI in acid solution. The two acetates, XIV and IIIa, which had previously been prepared from the reaction of acetyl bromide with I and II, respectively, proved to be diastereoisomers and showed that the opening of the α,β-epoxyketones with acetyl bromide in this instance is stereospecific and involved the same stereochemistry as the opening with hydrogen bromide.

Previous studies have resulted in the elucidation of the structure and stereochemistry of the halodiphenacyls.[3–6] Thus α-, and β-bromodiphenacyl were shown to be I and II, respectively, and the facile isomerization of the α-isomer (I) to the β-isomer (II) with base has been discussed.[4,6]

The conversion of II to I by reaction with hydrogen bromide followed by treatment of the adduct with ammonia has been reported.[6] The present re-

(1) Abstracted from the thesis of Mr. Richard G. Hiskey submitted in June 1955 to the Graduate School at Wayne State University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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(3) J. Berson, *J. Am. Chem. Soc.*, **74**, 5175 (1952).

(4) H. H. Wasserman, N. E. Aubrey, and H. E. Zimmerman, *J. Am. Chem. Soc.*, **75**, 96 (1953).

(5) C. L. Stevens, R. J. Church, and V. T. Traynelis, *J. Org. Chem.*, **19**, 522 (1954).

(6) C. L. Stevens and V. T. Traynelis, *J. Org. Chem.*, **19**, 522 (1954).

port describes the characterization and further chemical reactions of the adduct III.

The adduct III was obtained in 85% yield as previously reported.[5] An infrared spectrum of the adduct showed a hydroxyl stretching band and the ultraviolet spectrum showed the carbonyl group still in conjugation with the phenyl group. To establish the location of the hydroxyl group, the adduct was treated with sodium periodate in aqueous dioxane. The bromohydrin reacted slowly, consuming 1 equivalent of periodate in 49 hours. However, under the same conditions benzoin was completely oxidized in 45 minutes.

Acylation of the bromohydrin at 0° afforded an acetoxy derivative, m.p. 103°, in 86% yield. The same derivative has been previously prepared by heating β-bromodiphenacyl and acetyl bromide in a sealed tube at 100°.[7] Similarly the benzoate and tosylate derivatives could be prepared in 50–60% yield.

Confirmation of the α-hydroxyketone nature of the bromohydrin was obtained by oxidation with *N*-bromosuccinimide.[8] During the reaction, hydrogen bromide was evolved and succinimide was isolated in 99% yield. An infrared spectrum of the yellow reaction product showed the twin carbonyl absorption at 5.82 μ and 5.95 μ, indicative of an α-diketone.[9,10] The diketone proved to be thermally unstable even during molecular distillation, however bromine analysis on the crude reaction product indicated two bromine atoms to be present. Treatment of the dibromodiketone with sodium periodate yielded benzoic acid. All of these results are consistent with α-hydroxy-β-bromoketone III as the structure of the hydrogen bromide adduct. The assignment of III is in accord with the halohydrin resulting from the similar treatment of other α-ketooxides.[9,10]

Previously Church[11] reported the reaction of III with zinc in ethanol yielded a bromine free crystalline compound. The infrared spectrum of the debrominated product showed a hydroxyl stretching band and carbonyl absorption but no absorption in the 6.1 μ or 11.0 μ region. The same material IV could be prepared by treating the bromohydrin with sodium iodide in acetone at room temperature or by reaction with chromous chloride in acetone.

Treatment of the bromohydrin acetate (IIIa) with sodium iodide under similar conditions yielded the acetate derivative (IVa) of the debrominated material. The acetate prepared in this manner was identical in all respects to the derivative obtained directly from the debrominated alcohol IV.

That IVa did, in fact, contain a terminal methylene grouping was indicated by treatment with ozone, which afforded 1,3-diphenyl-2-acetoxypropane-1,3-dione (VII). These results were further substantiated by reduction experiments on IV. The compound readily adsorbed 2 moles of hydrogen and the product showed no carbonyl adsorption in the infrared spectrum. When the hydrogenation was stopped at 1 mole uptake, a clear liquid (V), presumably a mixture of diastereoisomers, was isolated. The infrared spectrum showed hydroxyl and carbonyl absorption and the ultraviolet spectrum indicated the carbonyl group to be in conjugation with a benzene ring.

Oxidation of V with sodium dichromate at 0° afforded the α-diketone VI. The material was assigned the structure of an α-diketone by the characteristic infrared spectrum and the conversion to 2-phenyl-3(1-phenylethyl)quinoxaline (VIII) with *o*-phenylenediamine.

When an ether solution of IV was saturated with dry hydrogen bromide at 0°, the same α-diketone VI resulted, as evidenced by a comparison of the infrared spectra and the quinoxaline derivatives VIII. The rearrangement product VI also resulted when an attempt was made to purify IV on alumina. Rearrangements of this nature (IV → VI) have been reported with other allylic alcohols containing a terminal methylene grouping.[12] When IVa was treated under the same conditions only unchanged acetoxyketone was recovered.

The structure of the α-hydroxyketone V, the α-diketone VI, obtained from oxidation of V and rearrangement of IV, and the quinoxaline derivative VIII of the α-diketone, were confirmed by two independent syntheses. In the first synthetic approach, dypnone (IX) was converted into 1,3-diphenylbutan-1-one (X). The ketone could be brominated in glacial acetic acid yielding a mixture of diastereomeric α-bromoketones XI which were separated by fractional crystallization into 59.4% of needles, m.p. 82–83°, and 23.5% of clusters, m.p., 120–121°. That the two compounds were α-brominated ketones and diastereoisomers, was demonstrated by the base catalyzed isomerization of the 82° isomer to the 120° isomer. Hydrolysis of either isomer of XI with refluxing alkali provided an impure liquid, similar in infrared and ultraviolet spectrum to Va. Oxidation of the hydrolysis product, followed by treatment with *o*-phenylenediamine, yielded 39% of VIII. The yield of VIII from V was 76.5%.

The fact that V obtained by hydrolysis of XI was impure was evident by the lower extinction coefficient in the ultraviolet spectrum and the low yield of quinozaline derivative and made another syntheses of V desirable. When phenylglyoxal

(7) C. Paal and H. Schultze, *Ber.*, **36**, 2386 (1903).

(8) M. Z. Barakat, M. F. Abd El-Wahab, and M. M. El-Sadr, *J. Am. Chem. Soc.*, **77**, 1670 (1955).

(9) H. O. House, *J. Am. Chem. Soc.*, **76**, 1235 (1954).

(10) H. H. Wasserman and N. E. Aubrey, *J. Am. Chem. Soc.*, **78**, 1726 (1956).

(11) R. J. Church, Thesis, Wayne University, 1952.

(12) (a) A. S. Dreiding and J. A. Hartman, *J. Am. Chem. Soc.*, **78**, 1216 (1956). (b) C. Djerassi, C. R. Smith, A. E. Lippman, S. Figdor, and J. Herran, *J. Am. Chem. Soc.*, **77**, 4801 (1955).

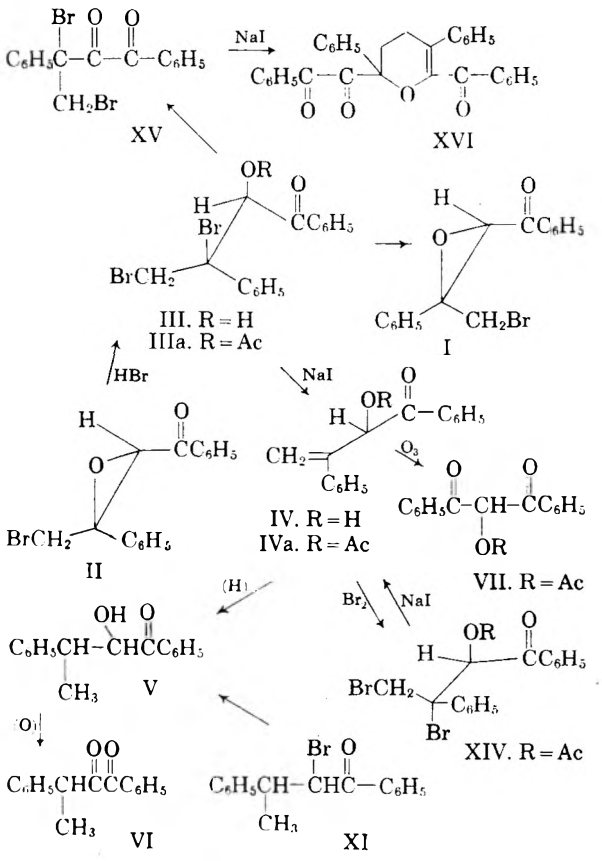
(XIII) was treated with α-phenylethylmagnesium chloride (XII), a 13.2% yield of clear liquid was obtained by molecular distillation. The Grignard product was identical in all respects to V and provided, on oxidation and quinoxaline formation, a 52.7% yield of VIII. The properties of V, VI, and VIII obtained by the second method were identical to those of the products arising from IV.

Bromination of IVa at 60° yielded a diastereometric dibromacetate XIV, m.p. 120–121°, in 81.4% yield. The same acetate was previously prepared by heating acetyl bromide and α-bromodiphenacyl in a sealed tube.[7] That the 103° acetate and the 120° acetate were diastereoisomers was demonstrated by their conversion to IVa with sodium iodide in acetone. Similar bromination of IV yielded only VI and not the expected β-bromohydrin.

A consideration of these data in view of the recent work from other laboratories cited below indicates that the stereochemical structure of the bromohydrin corresponds to that given in formula III. The *cis* nature of β-bromodiphenacyl (II) has been previously assigned[6] and the conversion of the bromohydrin III to the *trans*-α-bromodiphenacyl is also known.[5] Thus the reaction sequence II → III → I must involve one inversion or an odd number of inversions during the course of the two reactions. The *cis* acid catalyzed opening of epoxides has been discussed in some detail by Wasserman,[10] Brewster[13a] and Curtin,[13b] who provide certain well documented examples that clearly involve acid catalyzed *cis* opening of epoxides. The obvious structural similarity of the halodiphenacyls and the dypnone oxides of Wasserman,[10] together with the stereochemical requirement of the sequence II → III → I provides the basis for the stereochemical assignment of III, resulting from *cis* opening of the oxide II.

In this work I was treated with hydrogen bromide under the same conditions described for the β-isomer II, but no tractable product could be isolated. However, acetyl bromide is known to open each of the halodiphenacyls I and II to give different products. These products were shown to be diastereoisomers and not structural isomers and thus the reaction of acetyl bromide with the epoxides is stereospecific. Further, the acetate IIIa, which is formed from II, is related to III and indicates that this opening is a *cis*-opening of the epoxides.

When the dibromodiketone XV, from IIIa, was treated with sodium iodide the expected α,β-unsaturated diketone was not obtained, but rather a dimeric material was isolated. In analogy with other reported dimers from similar compounds[14] it is suggested that the structure is that of a substituted tetrahydropyran derivative such as XVI.



EXPERIMENTAL

α-3,4-Dibromo-1,3-diphenyl-2-hydroxybutan-1-one. β-Bromodiphenacyl II (m.p. 160–161°) was prepared in 54.7% yield according to the procedure of Wasserman *et al.*[4] A cold slurry of 15.8 g. (0.05 mole) of β-bromodiphenacyl in 150 ml. of dry ether was saturated with anhydrous hydrogen bromide for 4 hr. The white fluffy solid which formed was filtered and recrystallized twice from a petroleum ether–benzene mixture to yield 16.84 g. (85%) of α-3,4-dibromo-1,3-diphenyl-2-hydroxybutan-1- one (III), m.p. 144–145° (dec.).

Periodic oxidation of α-3,4-dibromo-1,3-diphenyl-2-hydroxybutan-1-one. To 1.1523 g. (2.89 millimoles) of bromohydrin III in 96 ml. of pure dioxane was added 50 ml. of a solution containing 10.5105 g. of sodium metaperiodate in 250 ml. of water. The mixture was diluted to 250 ml. and at intervals 10 ml aliquots were withdrawn and titrated with 0.1*M* sodium arsenite and 0.05*M* iodine solutions. After 49 hr. a sample containing 10 ml. standard arsenite solution consumed 2.90 ml. of standard iodine solution indicating 1.06 molar equivalents of periodate had reacted with 1.0 equivalent of sample. An aliquot withdrawn after 90 hr. indicated no further oxidation. Under the same conditions a 0.6153 g. (2.90 millimoles) sample of benzoin consumed 1.07 moles of periodate in approximately 45 min.

Reaction of III *with N-bromosuccinimide.* Following the procedure of Barakat *et al.*[8] a mixture of 4.0 g. (0.01 mole) of bromohydrin III and 1.78 g. (0.01 mole) of *N*-bromosuccinimide in 50 ml. of dry carbon tetrachloride was refluxed on a steam bath for 5 hr. After the evolution of hydrogen bromide ceased, 0.940 g. (94.9%) of succinimide, m.p. 123–124°, was removed by filtration. The solvent was removed *in vacuo* and the yellow liquid was taken up in 10 ml. of benzene, diluted with petroleum ether and 170 mg.

(13) (a) J. Brewster, *J. Am. Chem. Soc.*, **78**, 4061 (1956). And references cited. (b) D. Y. Curtin, A. Bradley, and Y. G. Hendrickson, *J. Am. Chem. Soc.*, **78**, 4064 (1956).

(14) (a) K. Alder and E. Ruden, *Ber.*, **74**, 920 (1941). (b) C. Mannich, *Ber.*, **74**, 557 (1941).

of white solid, probably unreacted bromohydrin, m.p. 120.5–122.5° (dec.) was removed by filtration. The benzene filtrate was concentrated *in vacuo* to yield 3.53 g. of the dibromodiketone as a viscous yellow liquid. The diketone could not be distilled without extensive decomposition even at low pressure. Bromine analysis on the crude liquid from oxidation indicated an impure dibromide. Although the analysis for bromine was not satisfactory for complete characterization, the ultraviolet spectrum exhibited an absorption peak at 261 mμ (ϵ_{max} = 11,200) and the infrared spectrum showed absorption at 5.82 μ and 5.95 μ indicating an α-diketone conjugated to a benzene nucleus.

α-3,4-Dibromo-1,3-diphenyl-2-acetoxybutan-1-one (IIIa). A solution prepared from 50 ml. of cold acetic anhydride containing 2 drops of perchloric acid and 10.0 g. (0.025 mole) of bromohydrin (IIIa) was stored at 0° for 40 hr. and then poured on ice. The mixture was neutralized in the cold with solid sodium carbonate and the solid which formed filtered, washed well with water and dried *in vacuo*. Two recrystallizations from petroleum ether–benzene afforded 9.5 g. (86.3%) of the bromohydrin acetate as white prisms m.p. 102–103°.[7] The acetate derivative proved quite unstable when exposed to light but could be stored several months in the dark at 10°.

Anal. Calcd. for $C_{18}H_{16}Br_2O_3$: C, 49.15; H, 3.67. Found: C, 48.85; H, 3.87.

The acetate could also be prepared in 86.3% yield using acetyl chloride and pyridine at 0°. A mixture melting point with samples from each method of preparation was not depressed.

The benzoate derivative could be prepared in 59.3% yield using benzoyl chloride and pyridine at 0°, m.p. 123–124°.

Anal. Calcd. for $C_{23}H_{18}Br_2O_3$: C, 55.00; H, 3.61. Found: C, 55.12; H, 3.42.

1,3-Diphenyl-2-hydroxybut-3-en-1-one (IV). To 5.0 g. (0.0125 mole) of bromohydrin (III) dissolved in 100 ml. of dry acetone was added a solution of 13 g. (0.086 mole) of dry sodium iodide in 120 ml. of dry acetone. The mixture was kept at room temperature for 14 hr. The precipitated sodium bromide was filtered, washed with dry acetone, and amounted to 2.55 g. (100%). The filtrate was decolorized with cold saturated sodium bisulfite solution, diluted to 1 l. with water and extracted four times with 50-ml. portions of ether. The combined ether extracts were washed once with water and dried over magnesium sulfate. After removal of the solvent *in vacuo*, a white crystalline solid was obtained, which after two recrystallizations from dilute methanol yielded 2.62 g. (87.9%) of 1,3-diphenyl-2-hydroxybut-3-ene-1-one, m.p. 80–82°.

An analytical sample recrystallized from methanol melted at 82–83°.

Anal. Calcd. for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found: C, 80.78; H, 6.09.

The debromination could also be accomplished in 80.3% yield when the bromohydrin was refluxed with zinc in ethanol or in 83.1% yield using chromous chloride[15] in acetone.

Rearrangement of 1,3-diphenyl-2-hydroxybut-3-en-1-one (IV) *to 1,3-diphenylbutane-1,2-dione* (VI). A solution containing 270 mg. (1.13 millimoles) of the unsaturated keto-alcohol (IVa), 10 ml. of 10% hydrochloric acid and 10 ml. of ethanol was heated at reflux for 3 hr. and then neutralized with *N* sodium hydroxide. The solution was extracted four times with 20-ml. portions of ether and the combined ether extracts washed with water and dried over magnesium sulfate. Removal of the solvent *in vacuo* yielded 260 mg. of 1,3-diphenylbutane-1,2-dione as a yellow liquid which was distilled through a small Hickman molecular still, b.p. 30°/0.001 mm.

Anal. Calcd. for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92 Found: C, 79.85; H, 6.02.

(15) G. Rosenkranz, O. Macera, J. Gatica, and C. Djerassi, *J. Am. Chem. Soc.*, **72**, 4077 (1950).

Recently this compound has been reported by Wasserman (ref. 10) from the isomerization of dypnone oxide and was characterized as the mono-2,4-dinitrophenylhydrazone, m.p. 196–197°.

The quinoxaline derivative (VIII) was prepared by refluxing 100 mg. (0.42 millimole) of the diketone (VI) and 55 mg. (0.5 millimole) of *o*-phenylenediamine in 3 ml. of glacial acetic acid for 45 min. The solution was diluted with 3 ml. of water and the solid recrystallized three times from dilute ethanol to yield 70 mg. (53.8%) of white needles m.p. 116–116.5°.

Anal. Calcd. for $C_{22}H_{18}N_2$: C, 85.12; H, 5.84. Found: C, 85.51; H, 5.52.

The ultraviolet spectrum exhibited absorption peaks at 323.5 mμ (ϵ_{max} = 10,300) and 239 mμ (ϵ_{max} = 34,300). Recently VIII has been prepared by treating the crude diketone (VI), obtained by the method of ref. 10, with *o*-phenylenediamine dihydrochloride in ethanol, and melted at 117.5–118.5°. The ultraviolet spectrum of this material exhibited absorption peaks at 239 mμ (ϵ_{max} = 35,400) and 323 mμ (ϵ_{max} = 10,300).[16]

Treatment of the diketone (VI) with sodium *meta*periodate in aqueous dioxane afforded a 50.2% yield of benzoic acid.

1,3-Diphenyl-2-hydroxybutan-1-one (V) A solution of 1.0 g. (4.2 millimoles) of 1,3-diphenyl-2-hydroxybut-3-en-1-one (IVa) in 20 ml. of ethyl acetate was hydrogenated in the presence of 100 mg. of 5% palladium on charcoal catalyst at room temperature and atmospheric pressure. The hydrogen uptake was stopped after 102 ml. (1 mole) of hydrogen was absorbed. Removal of the solvent *in vacuo* and distillation of the residue through a small Hickman molecular still yielded 0.87 g. (86.8%) of 1,3-diphenyl-2-hydroxybutan-1-one, b.p. 81° (0.5μ); n_D^{24} 1.5799.

Anal. Calcd. for $C_{16}H_{16}O_2$: C, 79.79; H, 6.70. Found: C, 79.90; H, 6.97.

The ultraviolet spectrum exhibited an absorption peak at 245 mμ (ϵ_{max} = 12,550).

1,3-Diphenylbutane-1,2-dione (VI) *from 1,3-diphenyl-2-hydroxy-butan-1-ene* (V). To 100 mg. (0.412 millimole) of the keto alcohol (V), obtained by reduction of 1,3-diphenyl-2-hydroxybut-3-ene-1-one (IV), in 5 ml. of glacial acetic acid was added a solution of 97.2 mg. (0.49 millimole) of sodium dichromate dihydrate in 10 ml. of glacial acetic acid. The solution was kept at room temperature for 20 hr. and the excess dichromate decomposed with 3 drops of methanol. The reaction mixture was poured into 300 ml. of water, extracted with ether and the combined ether extract washed with cold 5% sodium bicarbonate, water, and dried over magnesium sulfate. Removal of the solvent yielded 95 mg. of a yellow liquid whose infrared spectrum was identical with that of the α-diketone obtained by acid rearrangement of the unsaturated keto alcohol.

A quinoxaline derivative, prepared in the same manner, was obtained in 76.5% yield and melted at 115–116°. A mixture melting point with the quinoxaline obtained by acid rearrangement melted at 116.5–117°.

1,3-Diphenylbutan-1-one (X). A solution of 22.29 (0.1 mole) of dypnone (IX), prepared by the method of Muller and Spinose-Stockel[17] in 32% yield, was hydrogenated with 1.0 g. of platinum oxide in 250 ml. of ethyl acetate at 25° in a Parr apparatus. The hydrogen uptake was stopped at one mole. Removal of the solvent, followed by two recrystallizations from methanol yielded 13.5 g. (60.2%) of white plates, m.p. 73–74°.[18,19]

1,3-Diphenyl-2-bromobutan-1-one (XI). To 7.5 g. (0.033 mole) of 1,3-diphenylbutan-1-one (X) in 60 ml. of glacial

(16) H. O. House and D. J. Reif, *J. Am. Chem. Soc.*, **77**, 6525 (1955).

(17) A. Muller and G. Spinose-Stockel, *Osterr. Chem. Ztg.*, **49**, 130 (1948).

(18) E. P. Kohler and G. Heritage, *Am. Chem. J.*, **31**, 655 (1904).

(19) E. P. Kohler, *Am. Chem. J.*, **42**, 394 (1909).

acetic acid was added dropwise with stirring 5.34 g. (0.033 mole) of bromine in 10 ml. of glacial acetic acid. The solution was stirred for 20 min. and then poured on ice. The crude solid, 10.1 g., was filtered and fractionally crystallized from hexane. Two solids were obtained, one, 6.0 g. (59.4%), crystallized in needles, m.p. 82–83°, the other, 2.37 g. (23.5%), in clusters, m.p. 120–121°.[20]

Anal. Calcd. for $C_{16}H_{15}BrO$: C, 63.38; H, 4.99. Low melting isomer, found: C, 63.34; H, 5.01. High melting isomer, found: C, 63.22; H, 5.15.

Isomerization of the 1,3-diphenyl-2-bromobutanones. To 5.0 g. (0.016 mole) of the low-melting bromoketone was added a solution containing 1.28 g. (0.032 mole) of sodium hydroxide in 20 ml. of dioxane and 20 ml. of water. The solution was refluxed for 20 min., poured on ice, and extracted with ether. Removal of the solvent yielded 3.70 g. of a yellow oil which solidified to afford 0.500 g. (10%) of high melting isomer, m.p. 119–120°, and 2.92 g. (58.4%) of the low melting isomer.

1,3-Diphenyl-2-hydroxybutan-1-one from 1,3-diphenyl-2-bromobutan-1-one. A solution containing 2.09 g. (6.89 millimoles) of low-melting bromoketone, 0.50 g. (12.5 millimoles) of sodium hydroxide, 22 ml. of dioxane, and 10 ml. of water was refluxed for 1.5 hr., poured on ice, and extracted with ether. Removal of the solvent yielded 1.18 g. of yellow liquid which was distilled through a small Hickman molecular still, b.p., 80–90° at 0.001 mm. The infrared spectrum was similar but not completely identical with the keto-alcohol obtained by reduction of IV. Oxidation of the product from the bromoketone using the conditions previously described, followed by treatment with *o*-phenylenediamine in glacial acetic acid afforded a 38.4% yield of the quinoxaline derivative, m.p. 116.5–118°. A mixture melting point with the quinoxaline from reduction of oxidation of 1,3-diphenyl-2-hydroxybut-3-en-1-one (IV) was not depressed.

1,3-Diphenyl-2-hydroxybutan-1-one from phenylglyoxal. To 1.73 g. (0.071 g. atom) of magnesium turnings in 50 ml. of dry ether, under a nitrogen atmosphere, was added 10.0 g. (0.071 mole) of α-chloroethylbenzene in 100 ml. of dry ether, dropwise, with stirring, in 5 hr. The Grignard reagent was added, in 3 hr., with vigorous stirring, to a cold solution of 9.7 g. (0.07 mole) of phenylglyoxal in 200 ml. of dry ether in a nitrogen atmosphere. Hydrolysis with ammonium chloride solution, followed by ether extraction and removal of the solvent yielded 0.780 g. of solid, m.p. 152–153° (dec.) and 12.4 g. of yellow liquid. Trituration of the liquid with methanol, afforded 0.80 g. of *meso*-2,3-diphenylbutane, m.p. 122–124°. Distillation of 5.4 g. of the remaining liquid through a Hickman still yielded 1.07 g. of 1,3-diphenyl-2-hydroxybutan-1-one, b.p. 80° at 0.0005 mm., n_D^{25} 1.5694. The infrared spectrum was identical with the product from reduction and the ultraviolet spectrum exhibited an absorption peak at 246.5 mμ (ϵ_{max} = 12,400).

Oxidation of the keto alcohol prepared in this manner, followed by treatment with *o*-phenylenediamine gave the quinoxaline derivative (VIII), m.p. 116–117°, in 52.7% yield. The material was identical in all respects to the quinoxaline from the reduction and oxidation of IVa.

1,3-Diphenyl-2-acetoxybut-3-en-1-one (IVa). Following the procedure described for the preparation of IV, 9.0 g. (0.02 mole) of α-3,4-dibromo-1,3-diphenyl-2-acetoxybutan-1-one (IIIa) yielded 5.05 g. (90.1%) of 1,3-diphenyl-2-acetoxybut-3-ene-1-one, m.p. 80–84°, when treated with 20 g. of sodium iodide in acetone for 24 hr. Two recrystallizations from dilute ethanol raised the melting point to 85–86°. A mixture melting point with the acetate prepared from 1,3-diphenyl-2-hydroxybut-3-en-1-one with acetic anhydride and acetyl chloride[11] melted at 84–85°.

Anal. Calcd. for $C_{18}H_{16}O_3$: C, 77.15; H, 5.76. Found: C, 77.25; H, 5.87.

1,3-Diphenyl-2-acetoxybutan-1-one (Va). Using the same conditions described for the reduction of IVa 1.0 g. (3.5 millimoles) of the unsaturated ketoacetate yielded 0.740 g. (74%) of clear liquid, b.p. 70–80° (0.5μ), n_D^{25} 1.5571.

Anal. Calcd. for $C_{18}H_{18}O_3$: C, 76.57; H, 6.52. Found: C, 76.63; H, 6.64.

Ozonization of 1,3-diphenyl-2-acetoxybut-3-en-1-one (IVa). A solution of 0.636 g. (2.27 millimoles) of unsaturated acetoxyketone (IVb) in 30 ml. of ethyl acetate was cooled to −70° and saturated with ozone. After about 1 hr. the excess ozone was decomposed with 10% ferrous sulfate solution and the sample and trap solutions combined and distilled into 2,4-dinitrophenylhydrazine solution but no formaldehyde was detected. The aqueous distillation residue was extracted with ether and the extracts washed, dried, and evaporated to yield 0.100 g. (15.6%) of 1,3-diphenyl-2-acetoxypropane-1,3-dione, (VII), m.p. 92–94°.[21] A mixture melting point with an authentic sample was not depressed and the infrared spectra of the two materials were identical.

β-3,4-Dibromo-1,3-diphenyl-2-acetoxybutan-1-one (XIV). To 3.0 g. (10.8 millimoles) of 1,3-diphenyl-2-acetoxybut-3-ene-1-one (IVa) dissolved in 40 ml. of dry carbon tetrachloride, 1.8 g. (10.8 millimoles) of bromine was added dropwise, with stirring. The flask was illuminated with an infrared lamp during the bromination. Removal of the solvent yielded 4.65 g. of a white solid, which after two recrystallizations from petroleum ether afforded 3.87 g. (81.4%) of the β-bromohydrin acetate as white needles, m.p. 120–121°.

Anal. Calcd. for $C_{18}H_{16}Br_2O_3$: C, 49.15; H, 3.67. Found: C, 49.10; H, 4.05.

Regeneration of 1,3-diphenyl-2-acetoxybut-3-en-1-one (IVa) could be accomplished in 53.9% yield by treating the β-bromohydrin acetate with sodium iodide in acetone at room temperature for 26 hr. A mixture melting point with the unsaturated acetoxyketone from the α-bromohydrin acetate was not depressed and the infrared spectra were identical.

Bromination of 1,3-diphenyl-2-hydroxybut-3-ene-1-one under the same conditions gave only 1,3-diphenyl-butane-1,2-dione (VI) identical in all respects to the previous preparation.

Reaction of 3,4-dibromo-1,3-diphenylbutane-1,2-dione with sodium iodide. To 5.0 g. (12.6 millimoles) of dibromo diketone (XV) in 20 ml. of dry acetone was added a solution of 9.6 g. (6.40 millimoles) of dry sodium iodide in 40 ml. of dry acetone. After 2 hr. the solvent was removed *in vacuo* and the residue extracted with hexane until the extracts were no longer yellow. During the extraction several drops of acetone were added to prevent extraction of iodine. Removal of the solvent by vacuum afforded 3.0 g. of a yellow liquid which was titrated with methanol to yield 1.56 g. of dimer as dense yellow prisms, m.p. 132–134°.

Anal. Calcd. for $C_{32}H_{24}O_4$: C, 81.33; H, 5.12; mol. wt. 472. Found: C, 81.46; H, 5.15; mol. wt. (Rast) 524.

The ultraviolet spectrum exhibited an absorption peak at 250.5 mμ (ϵ_{max} = 26,200).

A quinoxaline derivative could be prepared in the manner previously described, m.p. 190.5–192.5°.

Anal. Calcd. for $C_{38}H_{28}N_2O_2$: C, 83.80; H, 5.18. Found: C, 83.60; H, 5.50.

The ultraviolet spectra exhibited absorption peaks at 322 mμ (ϵ_{max} = 10,900) and 239 mμ (ϵ_{max} = 56,300).

Bromination product of the dimer. To 200 mg. (0.42 millimoles) of the dimer (XVI) in 10 ml. of dry carbon tetrachloride was added 135 mg. (0.85 millimoles) of bromine in

(20) The bromoketone has been reported by T. S. Stevens, *J. Chem. Soc.*, 2114 (1930), m.p. 76°, by bromination of the ketone in carbon tetrachloride. When the reaction conditions were repeated a 68.2% yield of the low melting isomer was obtained, m.p. 77–80°.

(21) E. P. Kohler and J. L. E. Erickson, *J. Am. Chem. Soc.*, 53, 2308 (1931).

5 ml. of carbon tetrachloride. Light was applied from an infrared lamp and hydrogen bromide was copiously evolved. The solvent was removed *in vacuo* to yield a yellow oil which solidified on trituration with petroleum ether. Two recrystallizations from petroleum ether–benzene yielded 135 mg. (67.5%) of yellow needles, m.p. 162–163°. A test for bromine was negative.

Anal. Calcd. for $C_{32}H_{22}O_4$: C, 81.68; H, 4.71. Found: C, 81.35; H, 4.89.

The ultraviolet spectra exhibited absorption peaks at 250 mμ (ϵ_{min} = 30,550) and 357 mμ (ϵ_{max} = 16,500).

Acknowledgement. The authors wish to thank Mr. Robert French for the microanalyses and Dr. J. M. Vandenbelt, Parke, Davis and Company, for ultraviolet spectra.

DETROIT 2, MICH.

[CONTRIBUTION FROM THE RADIUM INSTITUTE OF THE UNIVERSITY OF PARIS]

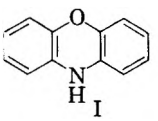
Preparation and Some Reactions of Phenoxazine and Phenoselenazine

PAULETTE MÜLLER, N. P. BUU-HOÏ, AND R. RIPS

Received July 25, 1958

Improved methods for the preparation of phenoxazine and phenoselenazines have been elaborated, and some reactions of these heterocycles have been investigated. Phenoselenazine and 2-chlorophenoselenazine readily underwent β-cyanoethylation; β-(10-phenoselenazyl)- and β-(2-chloro-10-phenoselenazyl)propionic acid, obtained on hydrolysis of the corresponding nitriles, were successfully cyclized to ketones derived from a new four-ringed nitrogen heterocycle.

Phenoxazine (I) and phenoselenazine (II) are two rarely investigated heterocycles, although they are isologs of phenothiazine, the nucleus of numerous dye-stuffs and pharmaceutical molecules. Recently, however, several phenoxazine derivatives have recaptured interest for their antitubercular activity,[1] and phenoselenazine itself is not devoid of pharmacological interest, since the selenium analogs of promethazine and chlorpromazine have shown antihistamine activity similar to that of their sulfur-containing analogs.[2] These observations prompted an investigation of the methods of



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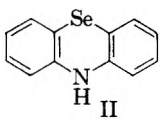
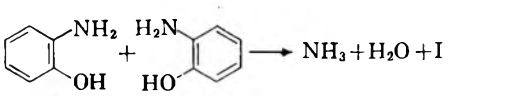


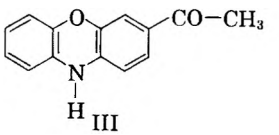
II

preparation of phenoxazine and phenoselenazine, and also of certain aspects of their chemical reactivity.

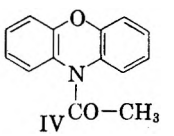
The classic method for preparing phenoxazine, involving the condensation of catechol with *o*-aminophenol,[3] necessitated the use of sealed tubes, and yields were very erratic. A far more convenient method has now been found to consist of the autocondensation of *o*-aminophenol in the presence of iodine according to the following equation:



This preparation of phenoxazine, which can be performed in open vessels and gives reliable yields, recalls the Knoevenagel method for synthesizing secondary diarylamines by iodine-catalyzed condensation of naphthols with primary arylamines.[4] Friedel-Crafts condensation of phenoxazine with acetyl chloride in the presence of aluminum chloride was found to give a monoketone, possibly 3-acetylphenoxazine (III), along with larger quantities of 10-acetylphenoxazine (IV). Position 3 is more probable than position 2, in view of the



III



IV

stronger orienting influence of the imino group.

The procedure described in the literature by Cornelius,[5] and later by Karrer,[6] for the preparation of phenoselenazine, which consisted of the condensation of diphenylamine with selenious chloride in benzene, has now been considerably improved by performing the reaction in chloroform, the use of this solvent allowing a better control of the reaction and enhancing the yield. The same method was also applied for preparing 2-chlorophenoselenazine; in both cases, the purity of the reaction products is greatly enhanced by vacuum-distillation prior to recrystallization.

Both phenoselenazine and 2-chlorophenoselenazine readily underwent β-cyanoethylation with acrylonitrile in the presence of benzyltrimethylammonium methoxide to give β-(10-phenoselenazyl)propionitrile (V) and β-(2-chloro-10-phenoselenazyl)propionitrile (VI). Thus, phenoselenazine

(1) *Cf.* B. Boothroyd and E. R. Clark, *J. Chem. Soc.*, 1499, 1504 (1953); these papers also give earlier relevant references.

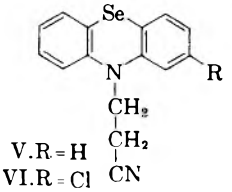
(2) P. Müller, N. P. Buu-Hoï, and R. Rips, unpublished results.

(3) A. Bernthsen, *Ber.*, 20, 943 (1887); F. Kehrmann, *Ann.*, 322, 9 (1902); phenoxazine was also prepared by heating *o*-aminophenol with its hydrochloride, by F. Kehrmann and A. A. Neil, *Ber.*, 47, 3102 (1914).

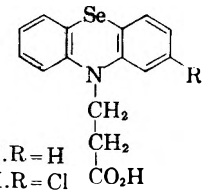
(4) E. Knoevenagel, *J. prakt. Chem.*, [2] 89, 17 (1914).

(5) W. Cornelius, *J. prakt. Chem.*, [2] 88, 398 (1913).

(6) P. Karrer, *Ber.*, 49, 603 (1916).

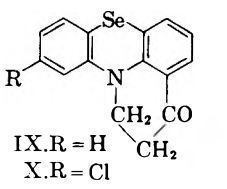


V.R = H
VI.R = Cl

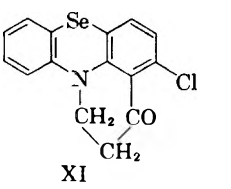


VII.R = H
VIII.R = Cl

and its nuclear substituted derivatives react in a similar manner to phenothiazine, which Smith[7] had already successfully β-cyanoethylated. These new propionitriles could be readily hydrolyzed with alcoholic sodium hydroxide, to give β-(10-phenoselenazyl)propionic acid (VII) and its 2-chloro derivative (VIII), although acid hydrolysis resulted in decomposition to the phenoselenazines. Like β-(10-phenothiazyl)propionic acid, which had been successfully converted into the corresponding cyclic ketone by means of phosphoric anhydride[7] or polyphosphoric acid,[8] β-(10-phenoselenazyl)propionic acid yielded, on similar treatment, 2,3-dihydro-3-keto-1*H*-pyrido[3,2,1-*kl*] phenoselenazine (IX); in contrast with the acid, which is colorless,



IX.R = H
X.R = Cl



XI

this ketone and its phenylhydrazone both showed a characteristic yellow color, similar to that of their analogs in the phenothiazine series. Cyclization of β-(2-chloro-10-phenoselenazyl) propionic acid similarly gave a yellow ketone, which could perhaps be assigned the structure X in preference to the isomeric structure XI, in view of the known deactivating influence and steric hindrance exerted by the chlorine atom in *ortho* position. In the case of β-(2-chloro-10-phenothiazinyl)propionic acid, Fujii[8] came to a similar conclusion as to the structure of the cyclization product.

10-Methylphenoselenazine, which Cornelius prepared by heating phenoselenazine with methyl iodide and methanol in a sealed tube,[5] was now more conveniently prepared, and in good yield, by methylating phenoselenazine by means of dimethyl sulfate in the presence of sodium hydroxide and in acetone medium; this method could also be applied to the *N*-methylation of phenoxazine.

EXPERIMENTAL

Preparation of phenoxazine. A mixture of 109 g. of *o*-aminophenol and 1 g. of pulverized iodine in a 500-ml. Claisen flask was heated slowly on a sand bath to 270–275° with removal of water, and heating was continued at that temperature for 4 hr. The hot reaction product was poured into a mortar, and the solid obtained on cooling was ground and extracted with toluene in a Soxhlet extraction apparatus; the toluene solution was washed with an aqueous solution of sodium hydrogen sulfite, then several times with aqueous sodium hydroxide to remove the unreacted *o*-aminophenol, and finally with water. After drying over sodium sulfate, the solvent was removed, and the residue distilled in a vacuum. Yield: 30–35% (27–32 g.) of *phenoxazine*, b.p. 215°/4 mm., crystallizing from ethanol in colorless needles.

Friedel-Crafts acetylation of phenoxazine. To a solution of 18 g. of phenoxazine and 13 g. of acetyl chloride in 250 ml. of carbon disulfide, 25 g. of powdered aluminum chloride was added in small portions with stirring. The mixture was kept for 4 hr. at room temperature, then refluxed on a water bath for 3 hr. After cooling, the reaction product was treated with ice and hydrochloric acid, and the organic material taken up in chloroform; the chloroform solution was washed with water and dried over sodium sulfate, the solvent was distilled off, and the residue vacuum-fractionated. A portion boiling at 215°/17 mm. consisted of 10 g. of *10-acetylphenoxazine*, crystallizing from ethanol in colorless prisms, m.p. 146°; the literature[9] gives m.p. 142°.

A higher-boiling portion consisted of 4.5 g. of a monoketone, probably *3-acetylphenoxazine*, b.p. 265–267°/17 mm., crystallizing from ethanol in bright yellow needles, m.p. 221°, giving a violet halochromy in sulfuric acid.

Anal. Calcd. for $C_{14}H_{11}NO_2$: C, 74.7; H, 4.9; N, 6.2. Found: C, 74.4; H, 5.0; N, 6.2.

Preparation of 2-chlorophenoselenazine. To a well-stirred solution of 49 g. of 2-chlorodiphenylamine (b.p. 185°/14 mm.) in 200 ml. of anhydrous chloroform, 77 g. of selenious chloride (prepared from selenious anhydride, powdered selenium, and hydrochloric acid in the presence of concentrated sulfuric acid, according to the method of Lenher and Kao[10]), dissolved in 100 ml. of chloroform, was added in small portions, and the mixture refluxed for 6 hr. After cooling, 100 ml. of chloroform was added, and the liquid obtained was filtered rapidly; the filtrate was then poured into water. The selenium formed was again filtered off, the chloroform solution was washed with aqueous sodium carbonate, then with water, and filtered, the organic layer dried over sodium sulfate, the solvent removed, and the residue vacuum-fractionated. Yield: 37 g. (52%) of *2-chlorophenoselenazine*, b.p. 225°/1 mm., crystallizing from ethanol in colorless needles, m.p. 200°.

Anal. Calcd. for $C_{12}H_8ClNSe$: Cl, 12.7; N, 5.0. Found: Cl, 12.4; N, 4.9.

Preparation of phenoselenazine and 10-methylphenoselenazine. Phenoselenazine, crystallizing from ethanol in shiny colorless needles, m.p. 195°, was prepared as above from diphenylamine, in 60–65% yield. To a solution of 22 g. of phenoselenazine and 7.1 g. of sodium hydroxide (dissolved in the minimum of water) in 170 ml. of acetone, 22 g. of dimethyl sulfate was added portionwise, with stirring. Stirring was continued for 1 hr., a further portion of sodium hydroxide was added, followed by the equivalent amount of dimethyl sulfate, and the mixture then left overnight. After evaporation of the acetone, water was added, the reaction product taken up in benzene, the benzene solution washed with water and dried over sodium sulfate, the solvent removed, and the residue vacuum-distilled (b.p. 195–200°/0.2 mm.), giving a 50% yield of *10-methylphenoselenazine*, colorless prisms, m.p. 139° (literature[6] m.p. 138–139°), from ethanol. The same procedure, applied to phenoxazine, afforded 10-methylphenoxazine, in similar yields.

β-(10-Phenoselenazyl)propionitrile (V). To a mixture of 22 g. of phenoselenazine and 27 ml. of acrylonitrile, 1 ml. of 40% benzyltrimethylammonium methoxide was added drop-

(7) N. L. Smith, *J. Org. Chem.*, **15**, 1125 (1950).

(8) K. Fujii, *Yakugaku Zasshi*, **77**, 1065 (1957); *Chem. Abstr.*, **52**, 5417 (1958).

(9) F. Kehrmann and A. Saager, *Ber.*, **36**, 477 (1903).

(10) V. Lenher and C. H. Kao, *J. Am. Chem. Soc.*, **47**, 772 (1925); N. P. Buu-Hoï and J. Lecocq, *Rev. sci.*, **82**, 39 (1944).

wise with stirring, whereupon a vigorous exothermic reaction set up. The red mixture was then refluxed for 1 hr. on a water bath; after cooling, the acrylonitrile in excess was distilled off in a vacuum, and the residue was recrystallized twice from acetone, giving a 75% yield of fine colorless needles, m.p. 163°. Like its sulfur analog, this nitrile was readily soluble in benzene and acetone, sparingly soluble in ethanol.

Anal. Calcd. for $C_{15}H_{12}N_2Se$: C, 60.2; H, 4.1; N, 9.4. Found: C, 60.2; H, 4.1; N, 9.4.

β-(2-Chloro-10-phenoselenazyl)propionitrile (VI). This nitrile was obtained in 75% yield from 15 g. of 2-chlorophenoselenazine and 19 ml. of acrylonitrile, as for the above. It crystallized from acetone in colorless prisms, m.p. 168°.

Anal. Calcd. for $C_{15}H_{11}ClN_2Se$: Cl, 10.6; N, 8.4. Found: Cl, 10.8; N, 8.5.

β-(10-Phenoselenazyl)propionic acid (VII). A solution of 22 g. of β-(10-phenoselenazyl)propionitrile and 18.5 g. of sodium hydroxide in 350 ml. of ethanol was gently refluxed for 15 hr.; after cooling, 500 ml. of water was added, a small amount of solid was filtered off, and the filtrate was acidified with dilute hydrochloric acid. The precipitate was recrystallized from ethanol, giving 16.5 g. of lustrous colorless leaflets, m.p. 193°.

Anal. Calcd. for $C_{15}H_{13}NO_2Se$: C, 56.7; H, 4.1; N, 4.4. Found: C, 56.7; H, 4.3; N, 4.4.

β-(2-Chloro-10-phenoselenazyl)propionic acid (VIII). Similarly prepared by hydrolysis of nitrile VI, this acid crystallized from ethanol in shiny colorless needles, m.p. 188°, giving a cherry red coloration in sulfuric acid.

Anal. Calcd. for $C_{15}H_{12}ClNO_2Se$: C, 51.1; H, 3.4; N, 4.0. Found: C, 51.1; H, 3.5; N, 4.1.

2,3-Dihydro-3-keto-1H-pyrido[3,2,1-kl]phenoselenazine (IX). To a solution of 5 g. of acid VII in 100 ml. of anhydrous benzene, 20 g. of phosphorus pentoxide was added and the mixture was refluxed for 1 hr. on a water bath. After cooling, the benzene was decanted from a dark solid mass, which was cautiously treated with ice, and the reaction product was taken up in benzene. The benzene solution was washed with aqueous sodium carbonate, then with water, dried over sodium sulfate, the solvent was distilled off, and the residue recrystallized several times from ethanol. Yield: 3 g. of shiny yellow needles, m.p. 115°, giving in sulfuric acid a blue halochromy rapidly turning pinkish orange.

Anal. Calcd. for $C_{15}H_{11}NOSe$: C, 60.1; H, 3.7; N, 4.7. Found: C, 60.0; H, 3.9; N, 4.6.

This ketone gave a *phenylhydrazone*, which crystallized from ethanol in shiny dark yellow leaflets, m.p. 180°.

10-Chloro-2,3-dihydro-3-keto-1H-pyrido[3,2,1-kl]phenoselenazine (X). This ketone, prepared in 70% yield by cyclization of acid VIII with phosphorus pentoxide, crystallized from ethanol in microscopic yellow needles, m.p. 146°, giving a brownish red halochromy in sulfuric acid. No isomeric ketone could be isolated, although in the preparation of the corresponding sulfur analog, Fujii[8] detected some of the isomer in the form of its oxime.

Anal. Calcd. for $C_{15}H_{10}ClNOSe$: C, 53.8; H, 3.0; N, 4.2 Found: C, 54.1; H, 3.2; N, 4.3.

Acknowledgment. Our thanks are due to Dr. Nathan L. Smith (University of Florida, Gainesville) for the gift of benzyltrimethylammonium methoxide used in this work. We are also indebted to Professors H. Maureu and P. Chovino and Dr. Lévy, of the Laboratoire Municipal (Paris), for several microanalyses.

PARIS V^e, FRANCE

[CONTRIBUTION FROM THE RADIUM INSTITUTE OF THE UNIVERSITY OF PARIS]

Orientation in Friedel-Crafts Acylations of 3-Chloro-2-methoxybiphenyl

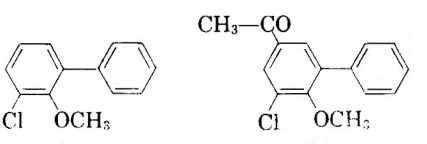
N. P. BUU-HOÏ AND LOUIS PETIT

Received August 20, 1958

Friedel-Crafts acetylation of 3-chloro-2-methoxybiphenyl is shown to occur in position 5 when the catalyst is stannic chloride, and in both positions 5 and 4′ when aluminum chloride is used. In the course of this investigation, a number of new derivatives of 3-chloro-2-methoxybiphenyl have been prepared.

As a part of a general study of biphenyl derivatives,[1] both theoretical (orientation problems) and practical (search for potential pharmaceuticals and germicides), the reactivity of 3-chloro-2-methoxybiphenyl (I) has been investigated.

It is known that Friedel-Crafts acylation of 2-methoxybiphenyl with acetyl chloride in the presence of aluminum chloride[2] occurs at position 5, and that other acid chlorides behave in the same way.[3] Hence it was of interest to investigate the orientation in similar reactions with 3-chloro-2-methoxybiphenyl. In this molecule, the presence of a chlorine atom in position 3 suggests that it would have a deactivating influence on position 5. the prospective site of



(I)

substitution, and, this being the case, then heteronuclear substitution, *e.g.* at position 4′, should also

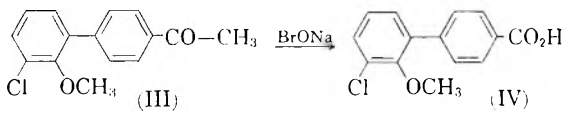
(1) *Cf.* N. P. Buu-Hoï and R. Royer, *Bull. soc. chim. France*, **17**, 489 (1950); *Rec. trav. chim.*, **70**, 825 (1951); N. P. Buu-Hoï, M. Sy, and J. Riché, *J. Org. Chem.*, **22**, 668 (1957); G. Viel, M. Sy, and N. P. Buu-Hoï, *Bull. soc. chim. biol.*, in press.

(2) K. von Auwers and G. Wittig, *J. prakt. Chem.*, **108**, 106 (1925).

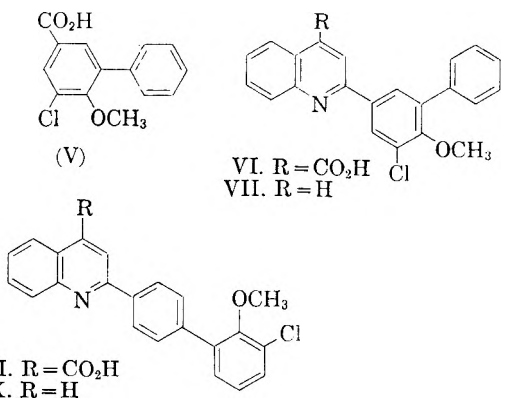
(3) *Cf.* N. P. Buu-Hoï and M. Sy, *J. Org. Chem.*, **21**, 136 (1956).

be expected to occur concurrently with the normal 5-substitution.

It is now found that the reaction between 3-chloro-2-methoxybiphenyl and acetyl chloride in the presence of aluminum chloride does in fact yield a mixture of two products, one a solid, m.p. 75°, the other an isomeric ketone which was liquid. The solid ketone proved to be 5-acetyl-3-chloro-2-methoxybiphenyl (II), as it was obtained in good yield and as sole product when, in place of aluminum chloride, stannic chloride was used; the latter is known to be a satisfactory catalyst for the acylation of phenol ethers but not for that of non-condensed aromatic hydrocarbons. The homogeneity of the liquid ketone to which the structure of 4′-acetyl-3-chloro-2-methoxybiphenyl (III) could thus be assigned,



was proven by its oxidation with sodium hypobromite to give only one acid, which was therefore 3-chloro-2-methoxybiphenyl-4′-carboxylic acid (IV). Oxidation of the solid ketone II under similar conditions afforded 3-chloro-2-methoxybiphenyl-5-carboxylic acid (V), whose high melting point (257°) is consistent with that of the corresponding nonchlorinated acid (m.p. 219°) previously reported.[3] Both ketones II and III readily underwent Pfitzinger reaction with isatin in the presence of potassium hydroxide to give 2-(3-chloro-2-methoxy-5-biphenylyl)- (VI) and 2-(3-chloro-2-methoxy-4′-biphenylyl)-cinchoninic acid (VIII), which underwent thermal decomposition to the corresponding quinolines VII and IX.



At variance with acetylation, in which the two isomeric ketones could be separated, aluminum chloride–catalyzed acylations with higher acid chlorides such as propionyl and butyryl chloride furnished liquid products, which were probably mixtures of ketones, but which could not be resolved. The same observation was made with benzoyl and phenacetyl chloride.

EXPERIMENTAL

Aluminum chloride–catalyzed acetylation of 3-chloro-2-methoxybiphenyl. To a water-cooled mixture of 22 g. of 3-chloro-2-methoxybiphenyl (prepared from the corresponding phenol by methylation with dimethyl sulfate and sodium hydroxide in aqueous methanol) and 14 g. of finely powdered aluminum chloride in 150 ml. of anhydrous carbon disulfide, 8.3 g. of acetyl chloride was added in small portions. After 12 hr. standing at room temperature, the mixture was heated on a warm water bath, and on cooling, decomposed with dilute hydrochloric acid. The reaction product was taken up in chloroform, washed with 10% aqueous sodium hydroxide, then with water, dried over calcium chloride, the solvents distilled off, and the residue vacuum-fractionated. Yield: 23 g. (88%) of a portion, b.p. 200–237°/20 mm., consisting of a ketonic mixture which crystallized partly after 45 days in the refrigerator.

(*a*) The crystalline portion (16 g.) was recrystallized several times from benzene plus petroleum ether, to give *5-acetyl-3-chloro-2-methoxybiphenyl* (II), shiny colorless prisms, m.p. 75°, giving a red halochromism with sulfuric acid.

Anal. Calcd. for $C_{15}H_{13}ClO_2$: C, 69.1; H, 5.0. Found: C, 69.2; H, 5.1.

(*b*) The liquid fraction was redistilled *in vacuo*, to give 6 g. of *4′-acetyl-3-chloro-2-methoxybiphenyl* (III), a pale yellow viscous oil, b.p. 231–235°/25 mm., n_D^{25} 1.6256, also giving a red halochromism with sulfuric acid.

Anal. Calcd. for $C_{15}H_{13}ClO_2$: C, 69.1; H, 5.0. Found: C, 68.9; H, 5.0.

Stannic chloride–catalyzed acetylation of 3-chloro-2-methoxybiphenyl. This reaction, performed as above with 26.5 g. of stannic chloride in place of aluminum chloride, afforded a 77% yield of a product which solidified completely, and gave on recrystallization from ethanol, ketone II, m.p. and mixed m.p. 75°.

3-Chloro-2-methoxybiphenyl-4′-carboxylic acid (IV). A solution of 2.6 g. of the liquid ketone (III) in dioxane was shaken with aqueous sodium hypobromite in excess, first at room temperature, then at 45–50°; the aqueous layer was extracted with chloroform and the excess of the oxidant was destroyed by addition of aqueous sodium hydrogen sulfite. The precipitate formed on acidification with hydrochloric acid was recrystallized from acetic acid, to give shiny colorless prisms, m.p. 172°; yield: 80%.

Anal. Calcd. for $C_{14}H_{11}ClO_3$: C, 64.0; H, 4.2. Found: C, 64.0; H, 4.3.

3-Chloro-2-methoxybiphenyl-5-carboxylic acid (V). Similar oxidation of the solid ketone (II) afforded an 80% yield of an acid, crystallizing from acetic acid in colorless, sublimable needles, m.p. 250°.

Anal. Calcd. for $C_{14}H_{11}ClO_3$: C, 64.0; H, 4.2. Found: C, 63.8; H, 4.3.

Pfitzinger reaction of ketone II. A solution of 2.6 g. of the ketone, 1.5 g. of isatin, and 1.5 g. of potassium hydroxide in 12 ml. of ethanol was refluxed for 78 hr.; after cooling, water was added and the neutral impurities extracted with ether. Acidification of the aqueous layer with acetic acid gave a precipitate of *2-(3-chloro-2-methoxy-5-biphenylyl)-cinchoninic acid* (VI), crystallizing from acetic acid in shiny yellowish prisms, m.p. 232°. Yield: 65%.

Anal. Calcd. for $C_{23}H_{16}ClNO_3$: C, 70.9; H, 4.2; N, 3.6. Found: C, 70.9; H, 4.2; N, 3.6.

Decarboxylation of this acid was effected by heating above its melting point, followed by vacuum-distillation of the reaction product; *2-(3-chloro-2-methoxy-5-biphenylyl)-quinoline* (VII) crystallized from ethanol in shiny colorless prisms, m.p. 201°. Yield: 80%.

Anal. Calcd. for $C_{22}H_{16}ClNO$: N, 4.1. Found: N, 4.1.

The corresponding *picrate* crystallized from ethanol in shiny yellow needles, m.p. 192°.

Anal. Calcd. for $C_{28}H_{19}ClN_4O_8$: C, 58.5; H, 3.3. Found: C, 58.4; H, 3.3.

Pfitzinger reaction of ketone III. The reaction with the liquid ketone (III) was performed in a similar manner, giving a 65% yield of *2-(3-chloro-2-methoxy-4'-biphenylyl)-cinchoninic acid* (VIII), crystallizing from acetic acid in yellowish prisms, m.p. 209°.

Anal. Calcd. for $C_{23}H_{16}ClNO_3$: Cl, 9.1. Found: Cl, 9.0.

2-(3-Chloro-2-methoxy-4'-biphenylyl)quinoline (IX), obtained on thermal decarboxylation of the above acid, crystallized from ethanol in shiny colorless prisms, m.p. 199°.

Anal. Calcd. for $C_{22}H_{16}ClNO$: N, 4.1. Found: N, 4.1.

The corresponding *picrate* crystallized from ethanol in bright yellow needles, m.p. 188°.

Anal. Calcd. for $C_{28}H_{19}ClN_4O_9$: N, 9.7. Found: N, 9.8.

Other acylations of 3-chloro-2-methoxybiphenyl. (*a*) Reaction of 22 g. of I with 9.8 g. of propionyl chloride in the presence of 14 g. of aluminum chloride furnished a 73% yield of *propionyl-3-chloro-2-methoxybiphenyl*, viscous, pale yellow oil, b.p. 230–235°/20 mm., which failed to solidify even partly, on standing in the refrigerator. Red halochromism forms with sulfuric acid.

Anal. Calcd. for $C_{16}H_{15}ClO_2$: C, 70.2; H, 5.5. Found: C, 69.8; H, 5.5.

(*b*) Similar reaction with 11.2 g. of butyryl chloride afforded a 69% yield of an oily *butyryl-3-chloro-2-methoxybiphenyl*, b.p. 230°/15 mm.

Anal. Calcd. for $C_{17}H_{17}ClO_2$: C, 70.7; H, 5.9. Found: C, 70.8; H, 5.8.

(*c*) With 14.7 g. of benzoyl chloride, the reaction gave a 77% yield of a viscous, oily ketone, b.p. 265–270°/16 mm.

Anal. Calcd. for $C_{20}H_{16}ClO_2$: C, 74.4; H, 4.7. Found: C, 74.6; H, 4.6.

(*d*) With 16.3 g. of phenacetyl chloride, the reaction gave a 68% yield of an oil, b.p. 270–280°/16 mm.

Anal. Calcd. for $C_{21}H_{17}ClO_2$: C, 74.9; H, 5.1. Found: C, 74.9; H, 5.0.

This last ketone mixture underwent a positive Pfitzinger reaction with isatin, to give in 68% yield and after 5 days' refluxing, a *cinchoninic acid*, crystallizing from acetic acid in yellowish prisms, m.p. 295°.

Anal. Calcd. for $C_{29}H_{20}ClNO_3$: C, 74.8; H, 4.3. Found: C, 74.5; H, 4.3.

The corresponding *quinoline* crystallized from ethanol in colorless needles, m.p. 164°.

Anal. Calcd. for $C_{28}H_{20}ClNO$: C, 79.7; H, 4.8. Found: C, 79.7; H, 4.8.

PARIS V^e, FRANCE

[CONTRIBUTION FROM THE UNIVERSITY OF CALIFORNIA, LOS ANGELES]

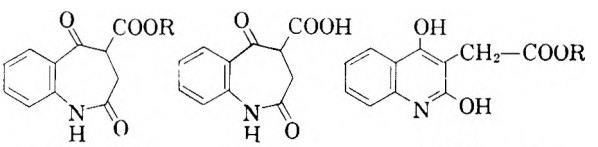
Rearrangement of Methyl 3-Azabenzocycloheptene-4,7-dione-6-carboxylate to 2,4-Dihydroxyquinoline-3-acetic Acid in Acid and Base

T. A. GEISSMAN AND A. K. CHO

Received July 11, 1958

The preparation of methyl 3-azabenzocycloheptene-4,7-dione-6-carboxylate (I) and its rearrangement in aqueous acid and base to 2,4-dihydroxyquinoline-3-acetic acid (III) are described. The quinoline structure of the rearrangement product is shown by its ultraviolet spectrum and by its conversion to dihydrodictamnine (VI). The ring closure of 2,4-dihydroxy-3-(2'-hydroxyethyl)quinoline to dihydrodictamnine was achieved in this work with sodium hydride and *p*-toluenesulfonyl chloride.

The azabenzocycloheptenedione (I) was prepared by carrying out a Dieckmann cyclization of methyl *N*- β-carbomethoxypropionylanthranilate with sodium in boiling toluene. The corresponding ethyl ester has been prepared recently by MacPhillamy *et al.*[1] who described the resistance to decarboxylation of the acid obtained by hydrolysis of Ia. A similar observation was made in the course of this work and an explanation for the stability of the product, assumed to be the β-ketoacid (II), was provided by investigation of the acid obtained by the basic and acid hydrolysis of the azabenzocycloheptenedione (I). The ultraviolet spectrum and subsequent reactions of the hydrolysis product showed it to be 2,4-dihydroxyquinoline-3-acetic acid (III). The ultraviolet spectrum of the hydrolysis product had double maxima in the 270 mμ and 300–340 mμ range, characteristic of 2,4-dihydroxyquinolines.[2]



I. R = CH_3
Ia. R = C_2H_5

II

III. R = H
IIIa. R = CH_3

Further evidence for the quinoline nature of the hydrolysis product was provided by its conversion to dihydrodictamnine (VI). This was accomplished by treating III with excess ethereal diazomethane to give 4-methoxy-2-hydroxyquinoline-3-acetic acid methyl ester (IV), which was reduced to 4-methoxy-2-hydroxy-3-(2'-hydroxyethyl)quinoline (V). Cooke[3] has prepared dictamnine using this approach but was able to obtain the quinoline acetic acid ester (IIIa) directly. Treatment of V with sodium hydride in tetrahydrofuran followed by *p*-toluenesulfonyl chloride[4] gave dihydrodictamnine.

(1) H. B. MacPhillamy, R. L. Dziemian, R. A. Lucas, and M. E. Kuehne, *J. Am. Chem. Soc.*, **80**, 2172 (1958).

(2) R. F. C. Brown, J. J. Hobbs, G. K. Hughes, and E. Ritchie, *Australian J. Chem.*, **7**, 348 (1954).

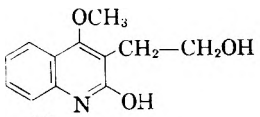
(3) R. G. Cooke and H. F. Haynes, *Australian J. Chem.*, **11**, 225 (1958).

(4) J. D. Roberts, W. Bennett, R. E. McMahon, and E. W. Holroyd, Jr., *J. Am. Chem. Soc.*, **74**, 4283 (1952).

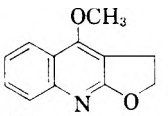
The ring closure to dihydrodictamnine was carried out by Cooke with polyphosphoric acid.

Treatment of I with excess ethereal diazomethane gave a methyl ether different from IV to which the structure VII was assigned. This reaction is consistent with the enolic spectral properties reported.[1] The enol ether VII was converted to the dihydroxyquinoline (IIIa) by the action of acid but treatment with aqueous base gave an acid, isomeric with IVa but which did not show the quinoline ultraviolet spectrum. The structure VIIa has been assigned to this acid.

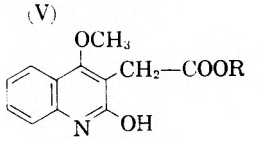
The conversion of I to III is a facile one, occurring in aqueous base or acid. A small quantity of the methyl ester of III was isolated as a side product from a large scale preparation of I.



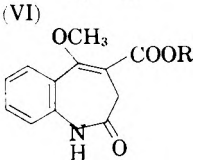
(V)



(VI)



IV. R = CH_3
IVa. R = H



VII. R = CH_3
VIIa. R = H

EXPERIMENTAL

Methyl 3-azabenzocycloheptene-4,7-dione-6-carboxylate (I). β-Carbomethoxypropionyl chloride was prepared as described by Cason and Rapoport.[5] A solution of all the acid chloride from 74 g. (0.55 mole) of methyl hydrogen succinate in 50 ml. of benzene was added dropwise with stirring and cooling to a solution of 75 g. (0.49 mole) of methyl anthranilate, and 40 g. (0.5 mole) of pyridine in 100 ml. of benzene. The mixture was allowed to stir at room temperature overnight, then it was washed with dilute acid, water, and aqueous sodium carbonate. The organic layer was evaporated at reduced pressure, and the residue upon cooling gave 66 g. (50%) of the acyl anthranilate, m.p. 67–70°, after recrystallization from ethanol.

A solution of 33 g. (0.123 mole) of the above mentioned amide in 100 ml. of toluene was added dropwise to 100 ml. of refluxing toluene containing 6 g. of sodium over a period of 1.5 hr. The reaction mixture was refluxed for 3.5 hr., then cooled and filtered. The tan precipitate was added to ethanol, neutralized with 6*N* HCl, and filtered. The resulting white flocculent precipitate was crystallized from ethanol, yielding 10.8 g. (38%) of fine needles melting at 222.5–224°. The ester I gave a dark purple coloration with ferric chloride. Infrared: 1670 cm.$^{-1}$, 1650 cm.$^{-1}$, 1610 cm.$^{-1}$; ultraviolet $\lambda_{max}^{ethanol}$: 227 mμ, log ε 4.36; 243 (sh) mμ, log ε 4.15; 295 mμ, log ε 3.98.

Anal. Calcd. for $C_{12}H_{11}O_4$: C, 61.79; H, 4.75; N, 6.00. Found: C, 62.05; H, 4.83; N, 6.16.

The methanol-water filtrate obtained from the isolation of the main product from a run using 50 g. of the acyl anthranilate was concentrated on the steam bath. The residue, a mixture of water and dark oil, was cooled and a crystalline solid formed. The solid was recrystallized from methanol and 1.8 g. of the ester (IIIa) melting at 185–190°, resolidifying and decomposing at 305–307° (dec.) were obtained. The ultraviolet spectrum of this compound showed typical 2,4-dihydroxyquinoline absorption. It gave a brown color with ferric chloride. Infrared: 1725 cm.$^{-1}$, 1710 cm.$^{-1}$, 1650 cm.$^{-1}$, 1635 cm.$^{-1}$, 1605 cm.$^{-1}$; ultraviolet $\lambda_{max}^{ethanol}$: 272 mμ, log ε 3.95; 282 mμ, log ε 3.92; 316 mμ, log ε 3.88; 328 mμ (sh), log ε 3.78.

Anal. Calcd. for $C_{12}H_{11}O_4N$: C, 61.79; H, 4.75. Found: C, 61.66; H, 4.91.

Methyl 4-methoxy-3-azabenzocyclohepta-1,5-dien-5-one-6-carboxylate. The ether solution of diazomethane from 17 g. of nitrosomethyl urea was added to a cooled suspension of 10 g. (0.042 mole) of I in 450 ml. of methanol and stirred with a magnetic stirrer. When the suspension became colorless, the ethereal diazomethane from another 17 g. of nitrosomethylurea was added. This process was repeated and the mixture was stirred overnight. The ice bath was allowed to melt during this period.

The excess diazomethane was decomposed with a few drops of glacial acetic acid and the clear solution was evaporated on the steam bath. The residue was recrystallized once from methanol and gave 10 g. (96%) of colorless plates, m.p. 145.5–146°. Infrared: 1665 cm.$^{-1}$, 1605 cm.$^{-1}$; ultraviolet $\lambda_{max}^{ethanol}$: 230 mμ, log ε 4.58; 282 mμ, log ε 4.10.

Anal. Calcd. for $C_{13}H_{13}O_4N$: C, 63.15; H, 5.30; OCH_3, 25.12. Found: C, 63.09; H, 5.28; OCH_3, 24.32.

2,4-Dihydroxyquinoline-3-acetic acid (III). A solution of 5 g. (0.021 mole) of I in 100 ml. of 5% aqueous potassium hydroxide was refluxed for 3 hr. The reaction mixture was cooled and made acid with dilute hydrochloric acid. The resulting precipitate was collected and recrystallized from ethanol, yielding 3 g. (64%) of the acid III melting at 290–295° (dec.). The melting point reported by MacPhillamy *et al.*[1] for this compound is 322–323° (dec.). Infrared: 1680 cm.$^{-1}$, 1650 cm.$^{-1}$, 1635 cm.$^{-1}$; ultraviolet $\lambda_{max}^{ethanol}$: 272 mμ, log ε 3.95; 281 mμ, log ε 3.95; 316 mμ, log ε 3.89; 326 mμ, log ε 3.80.

4-Methoxy-2-hydroxyquinoline-3-acetic acid methyl ester (IV). A suspension of 2 g. (0.0091 mole) of the acid III in ether was treated with an ethereal solution of diazomethane from 8 g. of nitrosomethylurea. The reaction mixture was initially cooled and stirred, and allowed to come to room temperature overnight. The excess diazomethane was decomposed with a few drops of glacial acetic acid and the solvent was removed by evaporation. Extraction of the residue with petroleum ether (b.p. 60–80°) and evaporation of the solvent gave crystals melting at 69–70°. The residue from the petroleum ether extract was recrystallized from ethanol. The weight of the latter fraction was 0.62 g. (30%) of the methyl ether ester (IV) melting at 171–171.5°. Infrared: 1725 cm.$^{-1}$, 1650 cm.$^{-1}$, 1605 cm.$^{-1}$; ultraviolet $\lambda_{max}^{ethanol}$: 269 mμ, log ε 3.86; 278 mμ, log ε 3.82; 324 mμ, log ε 3.86; 336 mμ (sh), log ε 3.69.

Anal. Calcd. for $C_{13}H_{13}O_4N$: C, 63.15; H, 5.30. Found: C, 62.81; H, 5.22.

Analytical data and ultraviolet spectrum indicated the material melting at 69–70° was 2,4-dimethoxyquinoline-3-acetic acid methyl ester.

Anal. Calcd. for $C_{14}H_{15}O_4N$: C, 64.36; H, 5.79. Found: C, 64.64; H, 5.50.

4-Methoxy-2-hydroxy-3-(2′-hydroxyethyl)quinoline (V). A solution of one g. (0.004 mole) of the ester IV in about 70 ml. of dry tetrahydrofuran was added with stirring to a solution of 0.29 g. (0.008 mole) of lithium aluminum hydride in 100 ml. of tetrahydrofuran at room temperature. The addition process took about 20 min. After the addition, the mixture was refluxed for 15 min. and cooled. A solution of 1 ml. of methanol in 9 ml. of tetrahydrofuran was added dropwise. This was followed by the dropwise addition of a solution of 1 ml. of water in 9 ml. of tetrahydrofuran. The reaction mixture was then filtered and the filtrate was evaporated under reduced pressure. The residue was a small quantity of oily material which did not crystallize after numerous attempts. The precipitate of the metal hydroxides

(5) J. Cason and H. Rapoport, *Laboratory Text in Organic Chemistry*, Prentice Hall Inc., New York, N. Y., 1950, p. 356.

was suspended in methanol and the suspension was saturated with carbon dioxide, heated, and filtered. This extraction process was repeated four times, and the combined extracts were evaporated at reduced pressure. The residue, a white solid, was extracted with chloroform. The chloroform extracts were evaporated and the residue was crystallized from methanol, yielding 0.4 g. (45.6%) of V, colorless needles, m.p. 179–180°.

Anal. Calcd. for $C_{12}H_{13}O_3N$: C, 65.74; H, 5.99. Found: C, 65.74; H, 6.15.

Dihydrodictamnine (VI). To a suspension of 0.02 g. (1 mmole) of sodium hydride in 25 ml. of tetrahydrofuran was added 0.2 g. (0.91 mmole) of 4-methoxy-2-hydroxy-3(2′-hydroxyethyl)quinoline. The resulting mixture was stirred overnight at room temperature. *p*-Toluenesulfonyl chloride (0.18 g., 0.94 mmole) was added at once and stirred for 1 hr. The excess reagents were decomposed by the addition of a few drops of water, followed by 5 ml. of dilute aqueous sodium hydroxide. This aqueous suspension was then stirred for an additional hour to ensure complete hydrolysis of the *p*-toluenesulfonyl chloride. The tetrahydrofuran was removed by distillation at reduced pressure and the aqueous residue was extracted three times with chloroform. The chloroform was evaporated on the steam bath, and the oily residue was extracted three times with boiling petroleum ether (b.p. 60–80°). Evaporation of the petroleum extracts and recrystallization of the residue from methanol-water gave 0.1 g. (55%) of dihydrodictamnine, m.p. 103–104.5°. (Reported[6] 103–104°.) Infrared: 1625 cm.$^{-1}$; ultraviolet $\lambda_{max}^{ethanol}$: 262 mμ, log ε 3.58; 272 mμ, log ε 3.67; 283 mμ, log ε 3.58; 308 mμ, log ε 3.40; 320 mμ, log ε 3.46.

(6) R. G. Cooke and H. F. Haynes, *Australian J. Chem.*, **7**, 273 (1954).

Anal. Calcd. for $C_{12}H_{11}O_2N$: C, 71.62; H, 5.51. Found: C, 71.62; H, 5.22.

Acid hydrolysis of methyl 3-azabenzocycloheptene-4,7-dione-6-carboxylate. A suspension of 2 g. (0.086 mole) of the ester I in 50 ml. of 4*N* sulfuric acid was refluxed for 3 hr. The reaction mixture was allowed to stand overnight and filtered. The precipitate was digested with methanol and filtered hot. The residue (1.0 g., 53.5%) was soluble in aqueous sodium bicarbonate and its infrared spectrum was identical with that of the quinoline carboxylic acid (III) melting at 295–300° (dec.). A mixed melting point with a sample of III prepared from basic hydrolysis was undepressed.

The methanolic filtrate from above was concentrated and cooled, giving crystals melting at 200–205°, which then solidified, remelting at 310–315°. This material was insoluble in sodium bicarbonate and its infrared and ultraviolet spectra were identical with the methyl ester of 2,4-dihydroxyquinoline-3-acetic acid (IIIa).

Anal. Calcd. for (IIIa) $C_{12}H_{11}O_4N$: C, 61.80; H, 4.75. Found: C, 61.56; H, 4.48.

Basic hydrolysis of the methylation product. A solution of 2 g. (0.081 mole) of the methyl ether of VII in 200 ml. of 2% aqueous sodium hydroxide was refluxed for 35 min. The reaction mixture was made acid with 6*N* hydrochloric acid and cooled. The crystals formed were collected by filtration and recrystallized from methanol, yielding 0.6 g. (32%) of the acid VIIa, melting at 215–217° with evolution of a gas. Infrared: 1710 cm.$^{-1}$, 1665 cm.$^{-1}$; ultraviolet $\lambda_{max}^{ethanol}$: 279 mμ, log ε 3.46.

Anal. Calcd. for (VIIa), $C_{12}H_{11}O_4N$: C, 61.80; H, 4.75. Found: C, 61.97; H, 4.65.

LOS ANGELES 24, CALIF.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

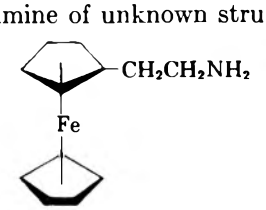
Structure of the Product of Anomalous Leuckart Reaction of 2-Ferrocylethylamine. A Route to 1,2-Disubstituted Ferrocenes[1]

DANIEL LEDNICER AND CHARLES R. HAUSER

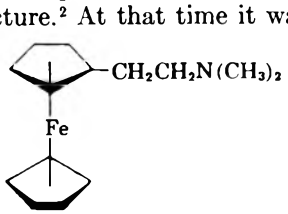
Received July 31, 1958

The product of the reaction of 2-ferrocylethylamine with formic acid and formaldehyde has been assigned the structure of the tetrahydroisoquinoline analog in the ferrocene series on the basis of degradative work. On treatment with strong base the methiodide of the cyclic product was opened to 1-*N*,*N*-dimethylaminomethyl-2-vinylferrocene. The structural features of the latter compound were demonstrated by spectra, hydrogenation, and displacement reactions.

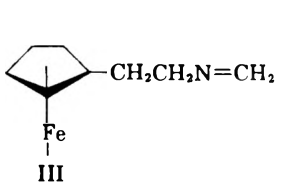
It has been recently reported that the treatment of the primary amine I with formic acid and formaldehyde under the conditions of the Eschweiler-Clarke modification of the Leuckart reaction affords instead of the expected product II, a tertiary amine of unknown structure.[2] At that time it was suggested that the presumably first formed intermediate III undergoes cyclization into the ferrocene ring. Such a ring closure would result in a product that had the structure IV. Osgerby and Pauson[3] have recently made the same suggestion.



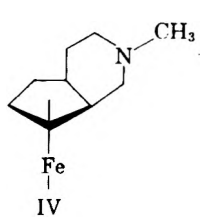
I



II



III



IV

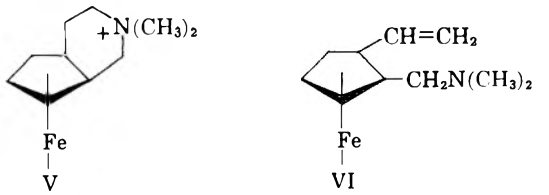
In the present work, the methiodide of the Eschweiler-Clarke reaction product was prepared as

(1) Supported by the Office of Ordnance Research, U.S. Army.

(2) D. Lednicer, J. K. Lidsay, and C. R. Hauser, *J. Org. Chem.*, **23**, 653 (1958).

(3) J. M. Osgerby and P. L. Pauson, *Chem. and Ind. (London)*, 196 (1958).

described previously.[2] In the earlier report[2] the reaction of that methiodide with potassium amide to afford a tertiary amine was described. The reaction was repeated to give that amine in an almost quantitative yield. If the methiodide is assigned the structure V, treatment with the strong base would be expected to lead to a β-elimination to form the unsaturated amine VI.

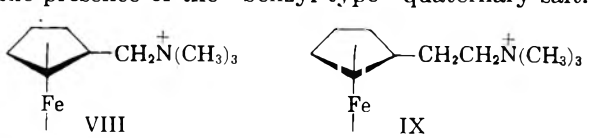


It was found that the spectral data were in good agreement with the structure VI. Thus the product exhibited a sharp infrared band at 6.1 μ as well as one at 11.1 μ characteristic of a terminal methylene. While alkylferrocenes exhibit rather featureless ultraviolet absorption spectra, VI was found to show the absorption maximum at 273 mμ characteristic of vinylferrocene.[4] The latter was taken as evidence that the double bond of VI was conjugated with the ring.

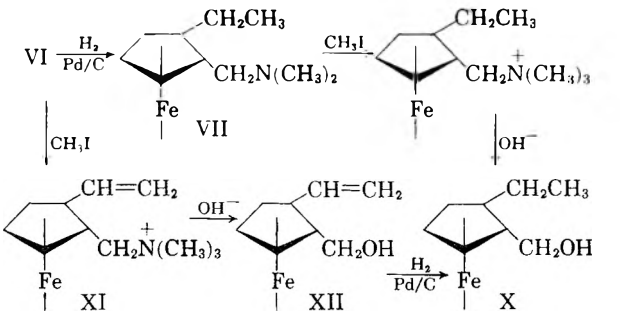
Treatment of the unsaturated amine VI with hydrogen over palladium-on-charcoal resulted in the uptake of an equivalent of the gas. The infrared spectrum of the resulting liquid amine, VII (see Scheme A) showed neither the band at 6.1 μ nor that at 11.1 μ. The 273 mμ band in the ultraviolet spectrum had similarly disappeared.

Although the above evidence for the presence of the conjugated vinyl group in VI leaves little choice for the formulation of the remainder of the molecule, it was nevertheless deemed desirable to demonstrate the presence of the "benzyl type" *N,N*-dimethylamino group.

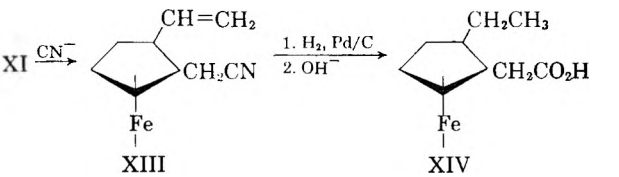
It is known that the methiodide of *N,N*-dimethylaminomethylferrocene (VIII) readily reacts with hydroxide ion[5] or cyanide ion[2] to lose trimethylamine and form the corresponding alcohol or nitrile. In connection with the present investigation it was found that the homologous quaternary salt IX is unaffected by cyanide ion, and in the presence of hydroxide ion undergoes slow β-elimination to form vinylferrocene. These reactions would thus seem to be a useful diagnostic test for the presence of the "benzyl type" quaternary salt.



Thus, it was found that treatment of the methiodide of the saturated amine VII with refluxing aqueous potassium hydroxide afforded the solid alcohol X. Similarly, the quaternary salt XI of the unsaturated amine VI produced on similar treatment the unsaturated alcohol XII. This product showed the same spectral earmarks (infrared bands at 6.1 μ and 11.1 μ and ultraviolet at 273 mμ) of the vinyl group as did the unsaturated amine VI. Catalytic reduction of XII resulted in the uptake of one equivalent of hydrogen. The product was shown by mixed melting point and infrared spectrum to be identical to X. The ultraviolet spectrum of this compound is the same as that of alkylferrocenes.



As further evidence for the ready displacement of trimethylamine from XI, this compound was treated with potassium cyanide. The liquid nitrile XIII which was obtained was reduced catalytically. The liquid saturated nitrile was in this case not purified but hydrolyzed directly to the acid XIV.



It is of interest that while ferrocylacetonitrile will readily undergo alkaline hydrolysis in refluxing ethanol,[2] these conditions did not appear to affect the 1-ethyl derrivative. The reaction of the sterically hindered compound was however achieved in good yield in refluxing alkaline aqueous ethylene glycol.

The experiments described above furnish evidence that in VI there are present a vinyl group and an *N,N*-dimethylaminomethyl group both of which are directly attached to the ferrocene ring. The fact that all the compounds in this series show infrared bands at 9 μ and 10 μ is taken as evidence that both groups are attached to the same ring.[6] Though the 1,2 relationship of the groups has not been proven, it is of interest that all these compounds show a very weak band at 10.5 μ which has been suggested to be characteristic of such disubstituted compounds.[7] The formation of a compound which has the structure of VI from the

(4) F. S. Arimoto and A. C. Haven, Jr., *J. Am. Chem. Soc.*, **77**, 6295 (1955).

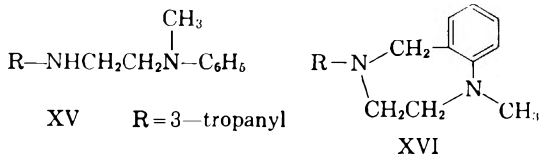
(5) J. K. Lindsay and C. R. Hauser, *J. Org. Chem.*, **22**, 355 (1957).

(6) M. Rosenblum, Ph.D. thesis, Harvard University, August 1953.

(7) K. K. Rinehart, Jr., K. L. Motz, and S. Moon, *J. Am. Chem. Soc.*, **79**, 2749 (1958).

quaternary salt V on treatment with base can be rationalized only by assuming the abnormal Leuckart reaction to have involved a cyclization to IV.

The cyclization of the intermediate III[8] is not without precedent. Thus, it is known that tetrahydroisoquinolines may be obtained from β-arylethylamines by treating the condensation products of the latter and formaldehyde with hydrochloric acid.[9] Subsequent to our original work[2] a report appeared describing the cyclization of XV to XVI upon treatment with formic acid and formaldehyde under the conditions of the Eschweiler-Clarke reaction.[10]



XV R = 3—tropanyl XVI

It should be mentioned that it has been observed that ferrocylbutyric acid under acid conditions likewise undergoes cyclization into the ring to which the acid is attached.[11]

Finally the product of the ring opening, VI, may prove of synthetic value, since it contains two readily transformable functional groups in the 1,2 positions of a single ring of ferrocene. In principle at least, by reducing the nitrile group of XIII (or of the dihydro compound) to the primary amine and subjecting this again to the conditions of the Eschweiler-Clarke reaction a 1,2,3-trisubstituted ferrocene might be obtained.

EXPERIMENTAL[12]

Reduction of 1-dimethylaminomethyl-2-vinylferrocene (VI) *to 1-dimethylaminomethyl-2-ethylferrocene.* A suspension of 5.46 g. (0.020 mole) of the unsaturated amine[13] and 0.50 g. of 10% palladium-on-charcoal in 25 ml. of methanol was stirred under hydrogen at atmospheric pressure. Within 15 min., 493 ml. (theo. 496 ml.) of hydrogen had been absorbed. The catalyst was removed by filtration and washed with methanol. The filtrates were then diluted with water (200 ml.) and the oily product taken up in ether. After drying over sodium sulfate the solvent was removed from the ethereal solution. The residual oil was dried *in vacuo* to afford 5.36 g. (98%) of the amine VII.

Anal. Calcd. for $C_{15}H_{21}FeN$: C, 66.43; H, 7.81; N, 5.17. Found: C, 66.42; H, 7.72; N, 5.11.

A small sample (0.25 g.) of the amine was treated with 5 ml. of saturated ethanolic picric acid. The orange powder which was deposited was recrystallized twice from ethanol to afford the picrate as red needles m.p. 162–162.5°.

Anal. Calcd. for $C_{21}H_{24}FeN_4O_7$: C, 50.43; H, 4.84; Fe, 11.16; N, 11.20. Found: C, 50.19; H, 4.74; Fe, 11.45; N, 11.26.

Methiodide of VII. A solution of 5.36 g. of the amine in 15 ml. of acetonitrile was cooled in an ice bath and treated with 5 ml. of methyl iodide. A solid was almost immediately deposited. The suspension was stored in the cold overnight. From this there was obtained 5.65 g. (70% of light yellow granules), m.p. 172–175° (dark 150°). Further crystallization lowered the m.p. to 170°.

1-Ethyl-2-hydroxymethylferrocene (X). A suspension of 5.20 g. (0.019 mole) of the methiodide obtained above in 52 ml. of 10% aqueous sodium hydroxide was brought to reflux. Almost immediately an oil began to separate and trimethylamine was evolved. At the end of 2.5 hr. the suspension was allowed to cool. The oil was taken up in ether and this solution washed with water and then dried over sodium sulfate. The oil which remained when the solvent was removed crystallized to a waxy solid on scratching. Recrystallization from hexane afforded the alcohol as a light orange solid (2.15 g., 47%), m.p. 42–52°. One further crystallization from the same solvent gave 1.76 g. of X, m.p. 54–56°.

1-Vinyl-2-hydroxymethylferrocene XII. A suspension of 11.0 g. of the quaternary salt XI[14] in 110 ml. of 10% aqueous sodium hydroxide was brought to reflux. Trimethylamine was evolved as a steam volatile oil separated. At the end of 2.5 hr. the reaction mixture was allowed to cool and worked up in the same manner as the displacement reaction of the saturated compound. The oil which remained when the solvent was removed was distilled at 2 mm. to yield 2.86 g. (44%) of a dark red liquid b.p. 149–153°. λ_{max}, 2.92 μ, 6.1 μ, 11.1 μ; 273 mμ; ϵ_{max} 7000.

Anal. Calcd. for $C_{13}H_{14}FeO$: C, 64.49; H, 5.83; Fe, 23.07. Found: C, 64.87; H, 5.64; Fe, 22.87.

A considerable amount of nonvolatile tar remained in the pot.

Catalytic reduction of XII *to 1-ethyl-2-hydroxymethylferrocene* (X). A suspension of 0.25 g. of palladium-on-charcoal in a solution of 2.84 g. of the alcohol XII in 15 ml. of methanol was stirred under hydrogen at atmospheric pressure. Within 20 min. the theoretical amount (266 ml. of hydrogen had been taken up. The catalyst was removed by filtration and washed with methanol. The filtrates were diluted to 150 ml. with water. On scratching the oil which came out of this solidified. The alcohol was obtained as 2.40 g. (84%) of orange solid, m.p. 48–53°. Two recrystallizations from hexane afforded 2.05 g. of X, m.p. 55–57°. The mixed melting point of this with alcohol obtained above by the displacement reaction was 55–56.5°. The infrared spectra of the two samples were superposable.

A sample was recrystallized further from hexane to afford long, fine, orange needles, m.p. 57–57.5°.

Anal. Calcd. for $C_{13}H_{16}FeO$: C, 63.96; H, 6.61; Fe, 22.88. Found: C, 64.26; H, 6.56; Fe, 22.99.

Reaction of the methiodide of 1-dimethylaminomethyl-2-vinylferrocene with potassium cyanide to form 2-vinylferrocylacetonitrile (XIII). To a solution of 30.0 g. of potassium cyanide in 300 ml. of water there was added 30 25 g. of the quaternary salt. As the reaction was brought to reflux an oil began to separate and the odor of trimethylamine was noted. At the end of 6.5 hr. the reaction was allowed to cool. The oil was taken up in ether and this solution washed with water and dried over sodium sulfate. The oil which remained on stripping the solvent was distilled at 1.4 mm. to afford 13.26 g. (72%) of the nitrile, b.p. 156–159°; λ_{max} 4.4 μ, 6.1 μ, 11.1 μ.

Anal. Calcd. for $C_{14}H_{13}FeN$: C, 66.96; H, 5.22; Fe, 22.24; N, 5.58. Found: C, 67.01; H, 5.39; Fe, 21.93; N, 5.95.

(8) Actually the intermediate in the cyclization is probably the protonation product of III bearing a positive charge on the terminal methylene group. That active intermediate could also be obtained by the loss of hydroxide from the methylol resulting from the addition of formaldehyde to the primary amine I.

(9) J. S. Buck, *J. Am. Chem. Soc.*, 56, 1769 (1934).

(10) S. Archer, T. R. Lewis, M. J. Unser, J. O. Hoppe, and H. Lape, *J. Am. Chem. Soc.*, 79, 5783 (1957).

(11) K. L. Rinehart, Jr., and R. J. Curby, Jr., *J. Am. Chem. Soc.*, 79, 3290 (1957).

(12) All melting points are uncorrected. Analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

(13) Prepared in the same manner as compound XV.[2]

(14) Quaternary salt, XI, is identical with and is prepared in the same manner as the methiodide of compound XV.[2]

Catalytic reduction of XIII *to 2-ethylferrocylacetonitrile.* A solution of 13.2 g. of the nitrile in 50 ml. of methanol containing in suspension 1.3 g. of 10% palladium-on-charcoal was stirred vigorously under hydrogen at atmospheric pressure. In 30 min., 1428 ml. (theo. 1330) of gas had been taken up. The reaction mixture was worked up in the same manner as the other reductions to afford 12.6 g. of a dark oil; λ_{max} 4.4 μ, no absorption at 6.1 μ or 11.1 μ.

Hydrolysis of the saturated nitrile to 1-ethylferrocylacetic acid. A solution of 12.6 g. of the nitrile obtained above and 48 ml. of 50% aqueous potassium hydroxide in 100 ml. of ethanol was brought to reflux. After 30 min. heating no ammonia had been noted. At this point 100 ml. of ethylene glycol was added to the solution and solvent was removed by distillation until the temperature of the distillate reached 100°. The now copious evolution of ammonia had ceased at the end of 2 hr. The hot solution was poured onto 800 ml. of ice water and this solution washed three times with 100 ml. of ether. The alkaline portion was subsequently filtered and acidified with phosphoric acid under a stream of nitrogen. The precipitated solid was collected on a filter, dried, and crystallized from benzene-hexane to afford 9.50 g. (70%) of the acid as stout amber rod-like crystals m.p. 123–125°.

Further crystallization from the same solvent pair gave a sample m.p. 124–125°.

Anal. Calcd. for $C_{14}H_{16}FeO_2$: C, 61.78; H, 6.13; Fe, 20.52. Found: C, 61.91; H, 6.20; Fe, 20.28.

Reaction of the methiodide IX *with sodium hydroxide.* A suspension of 5.0 g. of the quaternary salt[16] in 50 ml. of *N* sodium hydroxide was heated under reflux for 20 hr. At this temperature the salt went into solution. On cooling a crystalline solid came out of solution. This was collected on a filter and washed with ether to yield 3.70 g. (74%) of a material whose infrared spectrum was identical to that of starting material. The aqueous filtrate was extracted with ether and the organic solutions were combined. The residue obtained on removing the ether (0.08 g.) was chromatographed on an alumina column to afford 0.06 g. of a solid m.p. 46–52°, whose infrared spectrum is the same as that of vinylferrocene.

DURHAM, N. C.

(15) C. R. Hauser, J. K. Lindsay, and D. Lednicer, *J. Org. Chem.*, **23**, 358 (1958).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

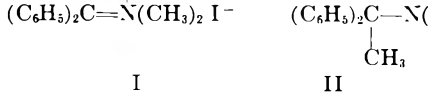
Addition Reactions of the Methiodide of Benzophenonemethylimine and Its 4-Methyl Analog with Nucleophilic Reagents[1]

CHARLES R. HAUSER AND DANIEL LEDNICER

Received August 5, 1958

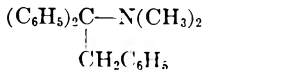
Benzophenone and 4-methylbenzophenone were condensed with methylamine to form the corresponding methylimines, which were converted to their methiodides. These methiodides were treated with potassium cyanide to give the corresponding α-aminonitriles. The α-aminonitrile from the methiodide of benzophenoneimine was obtained in low yield by the phenylation of the α-aminonitrile prepared from benzaldehyde, dimethylamine, and potassium cyanide. The methiodide of benzophenoneimine also underwent addition reactions with methylmagnesium iodide, potassio phenylacetonitrile, water, and liquid ammonia. The tertiary amine obtained from the methiodide and methylmagnesium iodide was prepared in better yield from the appropriate α-aminonitrile and the same Grignard reagent.

Some time ago, Sommelet[2] reported that the methiodide of benzophenonemethylimine (I) reacts with methylmagnesium iodide to form tertiary amine II, but the experimental details were not given.



I II

More recently, the corresponding reaction of the methiodide I with benzylmagnesium chloride was effected in this laboratory[3] as an independent synthesis of tertiary amine III, which had been obtained from a Stevens type of rearrangement.



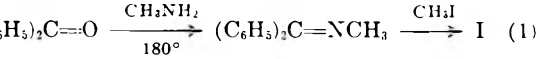
III

(1) Supported by the Office of Ordnance Research, U. S. Army.

(2) M. Sommelet, *Compt. rend.*, **183**, 302 (1926).

(3) C. R. Hauser, R. M. Manyk, W. R. Brasen, and P. L. Bayless, *J. Org. Chem.*, **20**, 1119 (1955).

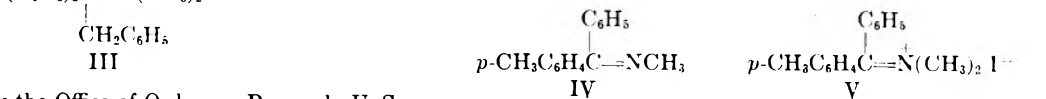
In the present investigation a further study along these lines was carried out. The methiodide I was prepared as indicated in Equation 1.[3]



(1)

The yield of the intermediate benzophenonemethylimine was 89%, which is somewhat higher than that (49%) reported previously.[3] The methiodide of this imine was obtained as an ether-insoluble, crystalline solid.

Similarly 4-methylbenzophenone was condensed in 68% yield with methylamine to give the corresponding imine IV, which was methylated to form the methiodide V.



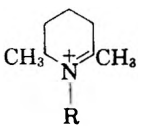
IV V

The methiodides I and V are ternary iminium salts whose cationic fragment may be represented by resonance forms such as Ia and Ib.

$$(C_6H_5)_2C{=}\overset{+}{N}(CH_3)_2 \longleftrightarrow (C_6H_5)_2\overset{+}{C}{-}N(CH_3)_2$$
Ia Ib

Since the cannonical form representing the carbonium ion Ib should make a significant contribution to the structure of the cation,[4] this ion might be expected to be especially reactive toward nucleophilic reagents. This expectation was borne out by the present results.

It should be mentioned that Leonard and coworkers[5] have recently shown in an excellent series of papers that such an alicyclic ternary ion as VI, which was prepared by oxidative dehydrogenation

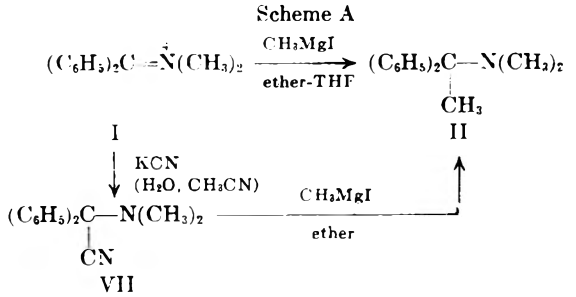


VI

of the corresponding substituted piperidine, likewise reacts readily with nucleophilic reagents including methylmagnesium iodide and potassium cyanide.

The cation Ia–b readily underwent addition reactions with methylmagneisum iodide in ether-tetrahydrofuran and with potassium cyanide in aqueous acetonitrile to form tertiary amine II and the α-aminonitrile VII in yields of 75% and 99% respectively (Scheme A).

Scheme A



The tetrahydrofuran was employed in the reaction with the Grignard reagent in order to facilitate solution of the ternary salt I. Actually the tertiary amine II was obtained in better over-all yield (95%) by first preparing the α-aminonitrile VII and then treating it with the same Grignard reagent in ether alone (see Scheme A). The latter step was realized in 96% yield. Both of these Grignard reactions were accompanied by transient purple colors.

The substitution type of reaction observed with the diphenylaminonitrile VII and the Grignard reagent (see Scheme A) is known[6] to be characteristic generally of such a monoarylaminonitrile as VIII, which is readily prepared from benzaldehyde, dimethylamine, and potassium cyanide (Equation 2).

$$C_6H_5CHO \xrightarrow[KCN]{(CH_3)_2NH} C_6H_5CH(CN){-}N(CH_3)_2 \qquad (2)$$
VIII

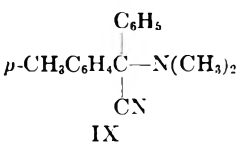
Incidentally, the corresponding direct preparation of the diphenylaminonitrile VII from benzophenone and these reagents appears not to have been realized.

In connection with the present work, the monophenylaminonitrile VIII was phenylated with bromobenzene by means of two molecular equivalents of potassium amide in liquid ammonia to form the diphenylaminonitrile VII in 25% yield (Equation 3).[7]

$$C_6H_5CH(CN){-}N(CH_3)_2 \xrightarrow[2.\ C_6H_5Br,\ KNH_2]{1.\ KNH_2\ (Liq.\ NH_3)} VII \qquad (3)$$
(VIII)

The procedure employed in this reaction was similar to that used by Leake and Levine[8] for the phenylation of certain carbanions, in which benzyne was considered to be an intermediate.

The preparation of the diphenylamnionitrile VII illustrated in Scheme A appears to be general. Thus the cation of the methiodide V similarly underwent the addition reaction with potassium cyanide to form the diarylaminonitrile IX in 93% yield.



IX

An attempt to resolve this asymmetric aminonitrile by means of D - 10 - camphorsulfonic acid was unsuccessful because of the ease with which this nitrile undergoes hydrolysis. Thus with one-half an equivalent of the acid, 4-methylbenzophenone was obtained from IX along with optically inactive recovered starting material. Similarly, treatment of the aminonitrile with ethanolic picric acid led to the isolation of the picrate of dimethylamine rather than that of IX.

The cation of the methiodide I underwent ready reaction with the carbanion of phenylacetonitrile in tetrahydrofuran. The product of this reaction, which was obtained in good yield, is formulated as the β-aminonitrile X (Equation 4).

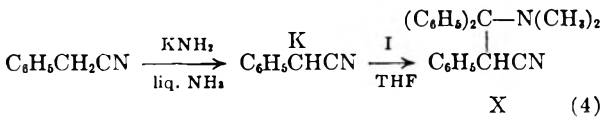
(4) Since the methiodide I has salt-like properties, the possible addition of the iodide anion to the cation to form an ether-soluble halide appears not to occur appreciably.

(5) See N. J. Leonard and F. Hanck, Jr., *J. Am. Chem. Soc.*, **79**, 5279 (1957).

(6) L. H. Goodson and H. Christopher, *J. Am. Chem. Soc.*, **72**, 358 (1950).

(7) The alkylation of the monophenylaminonitrile VIII with benzyl chloride has been accomplished by means of an equivalent of potassium amide in liquid ammonia to give a 90% yield of the benzylation product, which underwent dehydrocyanation on further treatment with the alkali amide or even on distillation to form the corresponding enamine; unpublished result of G. T. Ledford and C. R. Hauser.

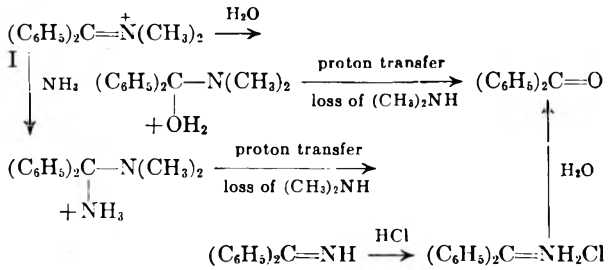
(8) W. W. Leake and R. Levine, abstracts of the ACS meeting, New York, September 1957, p. 37.



Unsuccessful attempts were made to effect the elimination of dimethylamine from X to form the corresponding acrylonitrile.

Finally the cation of the methiodide I reacted quite readily with water at room temperature and with liquid ammonia at −33° to form benzophenone and benzophenoneimine respectively. Presumably the water and ammonia functioned as nucleophilic reagents in these reactions to form intermediate addition complexes which then eliminated dimethylamine or the dimethylammonium ion to give the products isolated (Scheme B).

Scheme B



EXPERIMENTAL[9]

Conversion of the ketones to the imines. A stream of methylamine was passed through a melt of the appropriate ketone maintained at 180–185°. At the end of about 10 hr., the evolution of water had ceased. The oily product was allowed to cool and dissolved in ether. This solution was then quickly extracted with ice cold 2*N* hydrochloric acid. Each portion of the extract was immediately made alkaline with 40% sodium hydroxide. The resulting oil was extracted with ether, dried, and the solvent removed *in vacuo*. The pure imine was obtained by distillation at reduced pressure.

Benzophenone (66.5 g. ,0.36 mole), when subjected to this treatment afforded 55.3 g. (82%) of the imine as a colorless oil, b.p. 126–128° at 2.5 mm.; lit. 93° at 0.4 mm.

In the same way, 50.0 g. (0.25 mole) of 4-methylbenzophenone afforded 38.8 g. (68%) of IV as a clear oil, b.p. 140–142° at 2.4 mm. A small amount (5.1 g., 10%) of starting material was recovered from the neutral portion. A sample was redistilled to afford the analytical sample, b.p. 138–140° at 2.4 mm.

Anal. Calcd. for $C_{15}H_{15}N$: C, 86.08; H, 7.22; N, 6.69. Found C, 86.31; H, 7.36; N, 6.70.

Preparation of the ternary iminium salts. (*a*) *From benzophenone imine.* The liquid imine (62.7 g., 0.32 mole) was mixed with 30 ml. (0.48 mole) of methyl iodide. Within about 1 hr. the solution had set to a hard cake. After standing overnight, the yellowish solid was pulverized and washed well with ether to give 103 g. of I. The solid on heating slowly decomposes without showing a reproducible melting or decomposition point.

(*b*) *From 4-methylbenzophenone imine (IV).* Methyl iodide (21 ml., 0.34 mole) was added to 38.0 g. of the imine IV. Heat was evolved as an extremely viscous sirup V formed. Various attempts at crystallizing this taffy-like sirup were unsuccessful. This product was used without further purification.

(9) All melting points are uncorrected. Analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

α-Dimethylaminodiphenylacetonitrile VII. (*a*) *From the ternary salt.* A solution of 9.75 g. (0.29 mole) of the ternary salt from benzophenone (I) in 50 ml. of acetonitrile was added to a well stirred solution of 10 g. of potassium cyanide in 200 ml. of water. A solid came out almost immediately. After a total contact time of 30 min. the solid was removed by filtration and dried to yield 6.71 g. (99%) of the aminonitrile VII, m.p. 98–99.5°. The mixed melting point of this with a sample prepared by the direct phenylation was 98–99°.

(*b*) *By direct phenylation.* A solution of 48.0 g. (0.30 mole) of the aminonitrile of benzaldehyde in 50 ml. of ether was added to 0.3 mole of potassium amide (from 11.7 g. of the metal) in 300 ml. of liquid ammonia. To the resulting dark green solution there was added 47.1 g. (0.30 mole) of bromo benzene in 50 ml. of ether. Over the period of 25 min. another equivalent of potassium amide in 300 ml. of liquid ammonia was added to the reaction mixture by means of an inverse addition flask. The brown mixture was then stirred for an additional 5 min. and the base destroyed with 18 g. of ammonium chloride. The mixture was then taken to dryness on the steam bath. The grayish residue was washed with ether and these extracts separated from the inorganic salts by filtration. The solvent was removed from the ethereal solution to leave a dark oil. On standing the product separated from this oil as large cubic crystals. One crystallization from hexane afforded 18.2 g. (25%) of the aminonitrile VII, m.p. 99–100°.

A sample of this was recrystallized again from the same solvent to afford the analytical sample, m.p. 99–100°.

Anal. Calcd. for $C_{16}N_{16}N_2$: C, 81.32; H, 6.83; N, 11.86. Found: C, 81.50; H, 7.06; N, 11.88.

Formation of tertiary amine II. (*a*) *From the ternary salt.* Methylmagnesium iodide was prepared from 7.8 g. (0.055 mole) of methyl iodide and 1.34 g. of magnesium in 50 ml. of ether. To this solution there was then added 80 ml. of tetrahydrofuran. The solid salt I (8.3 g.)was added to this from a flask by means of Gooch tubing. A grape juice colored suspension developed immediately. Within 10 min. the intense coloration faded to light yellow. At the end of 2 hr. water was added and the ethereal layer separated. The aqueous portion was again extracted with ether. The combined organic solutions were then washed with 3 portions of 60 ml. of 3*N* hydrochloric acid. The oil which came out on making the washes alkaline was taken up in ether and dried. The solvent was then removed to leave behind 4.85 g. (85%) of the tertiary amine m.p. 27–30°. This solid was recrystallized twice from low boiling petroleum ether (cooling in Dry Ice–acetone) to afford 4.29 g. (75%) of crystalline solid, m.p. 40–41°.

The analytical sample, m.p. 40–41°, was obtained by one further crystallization in the same manner.

Anal. Calcd. for $C_{16}H_{19}N$: C, 85.28; H, 8.50; N, 6.22 Found: C, 85.11; H, 8.39; N, 6.30.

The picrate was formed in the usual manner from 0.25 g. of the amine and 5 ml. of saturated ethanolic picric acid and recrystallized from ethanol to a constant m.p. of 154–155°.

Anal. Calcd. for $C_{22}H_{22}N_4O_7$: 58.14; H, 4.88; N, 12.33. Found: C, 58.09; H, 5.24; N, 12.18.

(b) *From the aminonitrile.* A solution of 6.71 g. (0.029 mole) of the aminonitrile of benzophenone (VII) in 100 ml. of ether was added to 0.62 mole of methylmagnesium iodide in 100 ml. of ether. The addition was accompanied by gentle refluxing and the formation of a transient purple coloration. After 2 hr. stirring, 50 ml. of water was added to the colorless reaction mixture. The ethereal layer was separated, washed with water, and then extracted with two 90-ml. portions of dilute hydrochloric acid. The extract was then made strongly alkaline and the resulting oil taken into ether. Drying of the ethereal solution followed by evaporation of the solvent afforded the tertiary amine as an oil which on scratching yielded 6.12 g. (96%) of colorless crystals, m.p. 40–41°. The mixed melting point of this product with that obtained above was 40–41°.

Aminonitrile of 4-methylbenzophenone IX. A solution of the iminium salt V (prepared from 38.0 g. of the corresponding imine) in 180 ml. of acetonitrile was added to a stirred solution of 33.0 g. of potassium cyanide in 300 ml. of water. An oil almost immediately separated from the solution. At the end of 30 min. the oil was taken up in ether and the extract washed with water. The residue obtained when the solvent was removed from the dried extract was distilled at 2.0 mm. to afford 38.6 g. (91% based on imine) of the extremely viscous colorless product, b.p. 158–160°.

A sample was redistilled at the same pressure, b.p. 157–159°. All attempts to crystallize this very pure sample failed.

Anal. Calcd. for $C_{17}H_{16}N_2$: C, 81.56; H, 7.25; N, 11.19. Found: C, 81.31; H, 7.41; N, 10.94.

Reaction of the aminonitrile IX *with acids. (a) d-10-Camphorsulfonic acid.* A solution of 20.0 g. (0.08 mole) of the aminonitrile and 8.5 g. (0.037 mole) of the acid in 30 ml. of ethanol was warmed at reflux for 1 hr. The hot solution was then poured into water and the resulting oil taken into ether. The ethereal solution was washed with water, dried by percolation through sodium sulfate, and evaporated *in vacuo*. The residual oil was fractionally distilled at 2.2 mm. to afford 5.78 g. of 4-methylbenzophenone b.p. 147–150°, 5.06 g. of a middle cut b.p. 150–155°, and 5.03 g. of recovered starting material. The first cut was recrystallized first from ethanol and then from low boiling (30–60°) petroleum ether to afford the ketone of m.p. 54–55°, mixed melting point with an authentic smple, 54–55°.

The infrared spectrum of the high boiling sample was superimposable on one of the starting aminonitrile.

(b) Picric acid. A small sample of the aminonitrile was dissolved in a saturated ethanolic solution of picric acid. In 2 hr. large crystals slowly formed. The melting point of this picrate (158-160°) was not depressed on admixture with authentic sample of the picrate of dimethylamine.

Reaction of the ternary salt of benzophenone I *with potassio phenylacetonitrile.* A solution of 0.05 mole of potassium amide was prepared from 1.95 g. of the metal in 200 ml. of liquid ammonia. To this there was then added a solution of 5.85 g. (0.05 mole) of phenylacetonitrile in 50 ml. of tetrahydrofuran. An additional 150 ml. of tetrahydrofuran was then added to the green solution and the ammonia allowed to evaporate by bringing the solution to the reflux temperature of tetrahydrofuran. The tetrahydrofuran was allowed to distill over until free of the odor of ammonia. The salt (17.6 g. 0.05 mole) was then added from a flask through a piece of Gooch tubing. A transitory lavender color accompanied the exothermic reaction. At the end of an additional 1 hr. stirring, the solid was removed by filtration and washed with ether. The volume of the filtrate was reduced to about 50 ml. *in vacuo*, and this solution treated with ether. This solution was washed once with water and then extracted with concentrated hydrochloric acid. The acid solution was then made strongly alkaline with potassium hydroxide pellets, and the resulting solid collected by filtration. The crude product (13.5 g.) was recrystallized from hexane to afford 10.6 g. (62%) of colorless crystals of X, m.p. 132–140°. Since this product apparently decomposes on simply heating in ethanol, no picrate was prepared. When a sample was treated with an excess of methyl iodide in acetonitrile for 24 hr. the only isolable product was recovered starting material (53%).

A sample of the β-aminonitrile was recrystallized from cyclohexane to a constant m.p. of 142–144°.

Anal. Calcd. for $C_{23}H_{22}N_2$: C, 84,62; H, 6.79; N, 8.58. Found: C, 84.74, H, 6.75; N, 8.47

Reaction of the ternary salt I *with water.* One gram of the salt prepared from benzophenone was added to a small amount of water covered by ether. Within 20 min. the solid was completely in solution. The ethereal layer was separated, washed with water, and taken to dryness. Upon scratching, the residue afforded 0.45 g. (87%) of benzophenone, m.p. 45–46.5°; mixed melting point with authentic sample, 45–46°.

Reaction of the ternary salt I *with ammonia.* Two grams of the solid was added to 50 ml. of liquid ammonia in a potassium hydroxide drying tube protected flask. A white solid formed which slowly went into solution. The oil which remained when the ammonia had evaporated was washed with ether. The residue from the ether extracts (λ, 2.9μ, 3.0μ and 6.0μ) formed crystals from 10 ml. of dilute hydrochloric acid. Enough water (20 ml.) was added to produce a solution. On further standing, 0.92 g. (89%) of benzophenone, m.p. 45–46°, was deposited from the solution.

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[CONTRIBUTION FROM THE NATIONAL RESEARCH COUNCIL OF CANADA, PRAIRIE REGIONAL LABORATORY]

Hydrogenolysis of Carbohydrates. VI. Cyclic Ketals and Related Compounds

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Some alkylidene-sugar derivatives have been hydrogenolyzed using copper chromite catalyst in dioxane. Carbon-oxygen bonds in the 1,3-dioxolane rings of carbons-5 and -6 of 1,2-5,6-di-*O*-isopropylidene- and 1,2-5,6-di-*O*-cyclohexylidene-D-glucofuranoses being cleaved. *O*-Isopropylidene groups attached to the reducing center of a sugar molecule, however, do not hydrogenolyze to *O*-isopropyl derivatives in a similar manner. The 1,3-dioxolane ring of 1,6-anhydro-D-glucopyranose is split, reductive fission of the carbon-2 hydroxyl group also taking place. The inversion of configuration of hydroxyl groups under hydrogenolysis conditions is considered.

In the course of investigating possible applications of hydrogenolysis reactions to carbohydrate synthesis, various types of sugar derivatives are being investigated as substrates.[1] In a previous publication, 1,2-*O*-isopropylidene-D-glucofuranose was hydrogenated at 180° in dioxane using Adkin's copper chromite catalyst.[2] The main products were 1,2-*O*-isopropylidene-L-idofuranose and a crystalline 3,4-dideoxy-hexitol. In the present paper, the reactions of 1,2,5,6-di-*O*-isopropylidene- and 1,2-5,6-di-*O*-cyclohexylidene-D-glucofuranoses, 1,6-anhydro-D-

(1) Presented at the 134th meeting of the American Chemical Society, Chicago, September 1958; issued as N.R.C. No. 5013.

(2) P. A. J. Gorin and A. S. Perlin, *Can. J. Chem.*, **36**, 661 (1958).

glucopyranose.1 ,2-*O*-Isopropylidene-D-xylofuranose and 1,2-*O*-isopropylidene-D-fructopyranose under hydrogenolysis conditions are described.

Unlike the monosubstituted derivative, di-*O*-isopropylidene glucose was not affected at 180°, unchanged starting material being completely recovered. At 200°, however, degradation occurred and on acid hydrolysis of a portion of the reaction product, two reducing spots in addition to glucose were detected on a paper chromatogram using the *p*-anisidine hydrochloride spray.[3] Also, at least two other components, nonreducing to the *p*-anisidine spray, were detected on development with ammoniacal silver nitrate[4]; these minor products were not examined further. After crystallization of unchanged di-*O*-isopropylidene glucose the material in the mother liquor was hydrolyzed with acid and the reducing sugars produced were isolated by cellulose column chromatography.[5] The yields obtained were 7.5% (component having R_{Rh} 1.7) and 6.1% (R_{Rh} 2.0).[6]

The compound with R_{Rh} 1.7 was crystalline and a crystalline acetate and phenylosazone were derived. From physical and chemical determinations (see Experimental section) and by comparison with an authentic specimen, the sugar was shown to be 6-*O*-isopropyl-D-glucose. The other aldose, R_{Rh} 2.0, did not crystallize and was reduced with sodium borohydride[7] to the corresponding alcohol which was also a sirup, but gave a crystalline pentaacetate identical with synthetic penta-*O*-acetyl-6-*O*-isopropyl-L-iditol. The hydrogenolysis product was therefore 6-*O*-isopropyl-L-idose which must have been formed *via* inversion of the hydroxyl-group at C-5 (compare Ref. 2). Under more vigorous hydrogenolysis conditions (230–250°), 1,2-5,6-di-*O*-isopropylidene-D-glucofuranose was degraded to a unidentified mobile sirup.

A pattern of hydrogenolysis similar to that of 1,2-5,6-di-*O*-isopropylidene-D-glucofuranose at 200° was exhibited by 1,2-5,6-di-*O*-cyclohexylidene-D-glucofuranose. The products obtained after acid hydrolysis were crystalline 6-*O*-cyclohexyl-D-glucose identical to synthesized material and sirupy 6-*O*-cyclohexyl-L-idose characterized by conversion on sodium borohydride reduction to known 6-*O*-cyclohexyl-L-iditol. The yields of the two aldoses were lower than those of the *O*-isopropyl analogs.

The mode of hydrogenolysis of these 1,2-5,6-di-*O*-alkylidene-D-glucofuranoses appears to be a scission of the alkyl carbon-oxygen bond adjacent to C-5 to afford the 6-*O*-alkyl-1,2-*O*-isopropylidene-D-glucofuranose. The possibility of concomitant formation of 5-*O*-alkyl-derivatives by reductive cleavage of the bond adjacent to C-6 exists since the mixture of products may not have been separated completely. This cleavage of a 1,3-dioxolane ring is, perhaps, not surprising since some types of furan rings can be readily broken under similar hydrogenation conditions.[8] The inversion of configuration of hydroxyl groups on carbon atoms is a common feature of the action of copper chromite[2,9,10] and Raney nickel[11] on carbohydrates under hydrogenation conditions. It is suggested that this inversion is due to dehydrogenation to a ketone followed by reduction to the two possible stereoisomeric alcohols. Dunbar and Arnold[12] have shown that copper chromite dehydrogenates primary and secondary alcohols at 300–325° to aldehydes and ketones, respectively. Presumably, under the present conditions the dehydrogenating action of the catalyst is only lessened and not eliminated completely.

A similar type of reaction occurred when 1,6-anhydro-D-glucopyranose was hydrogenolyzed at 180°, no reaction occurring at 150°. Scission of the 1,3-dioxolane ring afforded 1,2-dihydro-D-glucal (at least 14.2%) and a smaller proportion of 1,2-dihydro-D-altral (5.1%) formed by hydroxyl-group inversion at C-3. The 1,6-*O*-linkage was, therefore, cleaved at the C-1 to oxygen bond with reduction of the hydroxyl group at C-2, no 1,5-anhydro-D-sorbitol being produced in the reaction. Under identical hydrogenation conditions dihydro-D-glucal is isomerized to dihydro-D-altral in 17% yield.[13]

Hydrogenolysis of 1,2-ketals was not detected with 1,2-*O*-isopropylidene- and 1,2-5,6-di-*O*-isopropylidene-D-glucofuranoses. Lack of reactivity was shown further by using 1,2-*O*-isopropylidene-D-fructopyranose (at 180°) and 1,2-*O*-isopropylidene-D-xylofuranose (at 200°) as substrates. In none of these instances were any derived 2-*O*-isopropyl polyols or isopropyl glycosides, formed by C-O bond scission, detected. In the last two cases, however, considerable hydroxyl-group inversion took place, three ketohexoses being detected chromatographically with urea oxalate spray on acid hydrolysis of the reaction product in the case of 1,2-*O*-isopropylidene-D-fructopyranose. 1,2-*O*-Isopropylidene-D-xylofuranose appeared to furnish a mixture of D-xylose (58%) and ribose (42%) on hydrogenation followed by acid hydrolysis. Thus extensive inversion at C-3 took place.

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6-*O*-Isopropyl-D-glucose, 6-*O*-cyclohexyl-D-glucose, penta-*O*-acetyl-6-*O*-isopropyl-L-iditol, and 6-*O*-cyclohexyl-L-iditol were synthesized as crystalline reference compounds in order to identify the hydrogenolysis products from the di-*O*-alkylidene-D-glucofuranoses. The steps used in the synthesis of these materials are outlined in the Experimental section. Dihydro-D-altral was synthesized from D-altrose according to general reaction procedures. The series of reactions, during which none of the intermediates were obtained crystalline, afforded a complex mixture which was fractionated on a cellulose column to give, in poor yield, dihydro-D-altral. The synthetic material was identical with a substance proved to be a 1,2-dihydro-hexital by von Rudloff and Tulloch, who obtained it by hydrogenolysis of α-methyl-D-glucopyranoside.[9] Although the yield of dihydro-D-altral from D-altrose was low the hydroxyl configuration was therefore established.

EXPERIMENTAL

All optical rotations were measured at 27°. Evaporations were carried out under reduced pressure using a bath temperature of 50°. Solvents used were butanol-ethanol-water (40:11:19 v./v.) for paper chromatograms and benzene-ethanol-water (500:50:1 v./v.) for cellulose column fractionations. Sprays used for developing paper chromatograms were *p*-anisidine hydrochloride and ammoniacal silver nitrate.

Hydrogenolysis of 1,2-5,6-di-O-isopropylidene-D-glucofuranose. Trial hydrogenations of di-*O*-isopropylidene glucose using copper chromite catalyst and dioxane as solvent indicated that under hydrogen pressures of 1000–2000 p.s.i. the substrate was unaffected at 180° and extensively degraded at 230–250°.

Di-*O*-isopropylidene glucose (150 g.) was dissolved in dioxane (2.5 l.) containing copper chromite catalyst (50 g.) and heated with shaking at 200° for 6 hr. under a hydrogen pressure of 1000–1500 p.s.i. The mixture was cooled, filtered, and evaporated to a sirup which crystallized from chloroform–light petroleum (b.p. 30–60°). The uncrystallizable residue (96 g.) obtained on evaporation of the mother liquor was dissolved in 0.1*N* sulfuric acid (500 cc) and the solution heated at 100° for 1 hr. The hydrolyzate was neutralized ($BaCO_3$), filtered, and evaporated to a sirup (55 g.) which afforded, as well as material corresponding to glucose, spots with R_{Rh} 1.7, 2.0, 2.2, and 2.4 on a paper chromatogram, the first two being reducing and the latter two nonreducing. The mixture was fractionated on cellulose columns to yield the material having R_{Rh} 1.7 (9.6 g.) and the compound having R_{Rh} 2.0 (7.8 g.). The nonreducing materials with R_{Rh} 2.2 and 2.4 (1.8 g.) were not further examined.

(*a*) R_{Rh} *1.7 Fraction.* The fraction crystallized and the material was recrystallized twice from methanol-ether and then from acetone and had m.p. 128–130° undepressed on mixing with authentic 6-*O*-isopropyl-D-glucose and $[\alpha]_D$ + 83° → + 47° (constant value: c 1.0, H_2O). Calculated for $C_9H_{18}O_6$: C, 48.6%; H, 8.2%. Found: C, 48.7%; H, 8.3%. The x-ray diffraction patterns of this material and 6-*O*-isopropyl-D-glucose were identical. The aldose had an alkaline iodine equivalent corresponding to a molecular weight of 218[14] and based on this figure and lead tetraacetate consumptions were: 1.62, 1.93, 1.99, and 2.08 moles after 3, 5, 11, and 26 min., respectively, thus indicating 5- or 6-substitution in the molecule.[15] The compound absorbed in the infrared in regions corresponding to isopropyl-substitution[16] and when the sugar was dealkylated[17] by heating for 10 min. in 42% hydrobromic acid at 100° the product, after neutralization (Ag_2CO_3) and evaporation, ran at the same speed as glucose on a paper chromatogram.

The derived phenylosazone of the sugar was prepared by heating the aldose (52 mg.) at 80° for 3 hr. in water (3 cc.) containing phenylhydrazine (0.10 cc.) and acetic acid (0.2 cc.). The yellow precipitate which formed on cooling was filtered off and recrystallized twice from methanol-benzene. It had m.p. 169–170° and $[\alpha]_D$ −107° → −67° (constant value: c, 0.7, pyridine). The 6-*O*-isopropyl-D-glucose phenylosazone had a molecular weight of 391 measured by the method of Barry, McCormick, and Mitchell.[18] It consumed 2.0 moles of sodium periodate after 15 and 30 min.[19] and produced 1 mole of formic acid when oxidized by lead tetraacetate in 90% acetic acid containing potassium acetate[20] thus proving 6-substitution. Calculated for $C_{21}H_{28}O_4N_4$: C, 63.0%; H, 7.1%. Found: C, 63.0%; H, 7.0%.

6-*O*-Isopropyl-D-glucose (30 mg.) was heated for 1 hr at 100° in acetic anhydride (1 cc.) containing sodium acetate (30 mg.). After adding to an excess of ice water, the mixture was left for 3 hr. and then extracted with benzene. The extract was washed twice with water and evaporated to a sirup which crystallized. Two crystallizations from light petroleum (b.p. 30–60°) afforded fine needles (15 mg.) of 1,2,3,4-tetra-*O*-acetyl-6-*O*-isopropyl-D-glucose with m.p. 124–125° and $[\alpha]_D$ +11° (*c*, 0.5, 2,4-lutidine).

Anal. Calcd. for $C_{17}H_{26}O_{10}$: C, 52.3%; H, 6.7%. Found: C, 52.3%; H, 6.6%.

(*b*) R_{Rh} *2.0 Fraction.* The sugar had $[\alpha]_D$ −13° (*c*, 2.1, H_2O) and could not be induced to crystallize. The compound (2.60 g.) was reduced in 3 hr. by an aqueous solution of sodium borohydride (1.20 g. in 200 cc.). Excess reagent was destroyed with acetic acid, the solution treated with Amberlite IR120, and evaporated to dryness. Repeated evaporations from the residue with methanol yielded a sirup (2.10 g.) containing 6-*O*-isopropyl-L-iditol.

The polyol (0.97 g.) was acetylated as described previously: the acetate crystallized and was recrystallized 3 times from ether-light petroleum (b.p. 30–60°). The pentaacetate had m.p. 87–88° and $[\alpha]_D$ −7.5° (*c*, 1.0 2,4-lutidine), the melting point was undepressed on mixing with penta-*O*-acetyl-6-*O*-isopropyl-L-iditol.

Anal. Calcd. for $C_{19}H_{30}O_{11}$: C, 52.5%; H, 7.0%. Found: C, 52.3%; H, 6.9%.

The x-ray diffraction pattern of the product was identical with that of an authentic specimen.

Hydrogenolysis of 1,2-5,6-di-O-cyclohexylidene-D-glucofuranose. Using the same hydrogenolysis and hydrolysis conditions as for the 1,2-5,6-di-*O*-isopropylidene-derivative, the cyclohexylidene-compound (25.0 g.) was converted to glucose and reducing materials of R_f's 0.58 and 0.70 on a paper chromatogram. The mixture was extracted continuously by chloroform from water. After a short time, the chloroform extract (0.90 gm.) contained mainly the compound with R_f 0.70 with a trace of the material with R_f 0.58 as well as some nonreducing material of high R_f. On prolonged extraction, the slower moving compound was obtained (0.53 g.). Fractionation on a cellulose column of

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the initial chloroform extract yielded 0.36 g. of the faster and 71 mg. of slower material. The overall yields corresponded to 2.4% and 1.4%, respectively, for the R_f 0.58 and 0.70 compounds.

(a) R_f 0.58 Fraction. The fraction crystallized and afforded 6-*O*-cyclohexyl-D-glucose, after two recrystallizations from acetone, which softened at 106° and melted at 115–117° (undepressed with authentic crystals) and had $[\alpha]_D$ +60° → +45° (constant value: *c*, 1 0 H_2O). Calculated for $2C_{12}H_{22}O_6.H_2O$: C, 53.1%; H, 8.5%. Found: C, 52.9%, H, 8.5%. Its x-ray diffraction pattern was identical to that of the known material.

(b) R_f 0.70 Fraction. The sirupy product did not crystallize and a portion (144 mg.) was dissolved in water (10 cc.) containing sodium borohydride (30 mg.). After 3 hr. the mixture was worked up as the earlier sodium borohydride reduction. The sirup (122 mg.), thus formed, deposited crystals from acetone and these were recrystallized twice from acetone. The melting point of the product was 78–80° not lowered on mixing with 6-*O*-cyclohexyl-L-iditol, and had $[\alpha]_D$ −5° (*c*, 1.1 sat. borax).

Anal. Calcd. for $C_{12}H_{24}O_6$: C, 54.5%; H, 9.2%. Found: C, 54.7%; H, 9.4%.

6-O-Cyclohexyl-L-iditol, obtained by hydrogenolysis and borohydride reduction, gave an x-ray diffraction pattern identical with that of the authentic compound.

Hydrogenolysis of 1,6-anhydro-D-glucopyranose. 1,6-Anhydro-D-glucopyranose (3.0 g.) was hydrogenated for 6 hr. at 180° in dioxane (150 cc.) containing copper chromite (1.0 g.) using a pressure of 1000–1500 p.s.i. After filtration and evaporation the resulting sirup (2.62 g) was examined on a paper chromatogram using ammoniacal silver nitrate as spray. The main spot had R_{Rh} 1.3 with smaller amounts at R_{Rh} 1.4, 1.8 and the starting material (R_{Rh} 1.1).

The mixture was fractionated on a cellulose column and the component having R_{Rh} 1.4 (0.14 gm.) crystallized and was recrystallized three times from ethyl acetate to give a substance having m.p. 105–106° (undepressed on admixture with dihydro-D-altral) and $[\alpha]_D$ +73° (*c*, 0.8 H_2O).

Anal. Calcd. for $C_6H_{12}O_4$: C, 48.6%; H, 8.2%. Found: C, 48.4%; H, 8.2%.

Its x-ray diffraction pattern was identical with that of dihydro-D-altral.

The next fraction having R_{Rh} 1.3 (0.39 g.) gave crystals with m.p. 87–88° after three recrystallizations from ethyl acetate and had $[\alpha]_D$ +19° (*c*, 1.0 H_2O).

Anal. Calcd. for $C_6H_{12}O_4$: C, 48.6%; H, 8.2%. Found: C, 48.3%; H, 8.2%.

The melting point was not depressed on mixing with dihydro-D-glucal, which gave an x-ray diffraction pattern identical with the hydrogenolysis product. A further fraction (0.55 gm.) was obtained from the column and contained a mixture of the compounds having R_{Rh}'s 1.1 and 1.3. No 1:5-anhydro-D-sorbitol was detectable in any fraction.

Hydrogenation of 1,2-O-isopropylidene-D-fructopyranose. 1,2-*O*-isopropylidene-D-fructopyranose (14.0 g.) was dissolved in dioxane (250 cc.) containing copper chromite (3.0 g.) and hydrogenated at 1500–2000 p.s.i. for 6 hr. at 180°. The solution was filtered and evaporated to a sirup (12.7 g.) which was hydrolyzed in 0.1*N* sulfuric acid (30 cc.) at 100° for 30 min. Neutralization ($BaCO_3$) followed by filtration and evaporation yielded a sirup which was shown to contain fructose and two other ketohexoses, moving faster than fructose on a paper chromatogram which gave blue colors with the urea oxalate spray.[21] A visual estimate of the proportion of the new sugars was about 15% of the whole ketose fraction. Also, a pink spot of R_{Rh} 1.0 was detected (brown on development with *p*-anisidine hydrochloride). When a chromatogram was sprayed with ammoniacal silver nitrate polyols of $R_{Rh} > 1.0$ were observed and these (0.62 g.) were fractionated on a cellulose column. However, these were shown to contain no isopropyl groups on examination with an infrared absorptionmeter. No material behaving as an isopropyl-ketoside was observed (on a paper chromatogram) since on acid hydrolysis of the hydrogenation product the spots did not disappear.

Hydrogenation of 1,2-O-isopropylidene-D-xylofuranose. The isopropylidene xylose (5.1 g.) was hydrogenated at 200° using the same procedure as above and the sirupy product (3.7 g.) was examined on a paper chromatogram using the *p*-anisidine hydrochloride and ammoniacal silver nitrate sprays. A small amount of nonreducing material (R_{Rh} 1.2) was detected before and after acid hydrolysis (in 0.1*N* H_2SO_4 for 1 hr. at 100°) and was shown to be present as 7.4% of the total by chromatography on cellulose. The remainder appeared to consist of a mixture of xylose and ribose (paper chromatographic examination) which contained 42% of the latter as shown by the orcinol–ferric chloride[22] method after the two components were separated by chromatography on filter paper strips.

The polyol fraction described did not give infrared absorption in the isopropyl region.

6-O-Isopropyl-D-glucose. 3-*O*-Benzyl-6-*O*-toluenesulfonyl-1,2-*O*-isopropylidene-D-glucofuranose[23] (3.83 g.) was heated under reflux in isopropanol (40 cc.) in which sodium (0.79 g.) had been dissolved. After 18 hr., benzene was added and the solution washed three times with water. Removal of solvent yielded a brown sirup (2.32 g.) with $[\alpha]_D$ −16° (*c*, 1.4 EtOH) which contained 3-*O*-benzyl-6-*O*-isopropyl-1,2-*O*-isopropylidene-D-glucofuranose.

A portion of the product (1.16 g.) was debenzylated by dissolving in methanol (50 cc.) containing Raney Nickel[23] and heating for 4 hr. at 70° under 1500 p.s.i. hydrogen pressure. The mixture was filtered and evaporated to a colorless sirup (0.67 g.) having $[\alpha]_D$ −14° (*c*, 1.9 EtOH).

The 6-*O*-isopropyl-1,2-*O*-isopropylidene-D-glucofuranose (0.48 g.) was hydrolyzed at 100° for 30 min. in 0.1*N* hydrochloric acid. The solution was neutralized (Ag_2CO_3), filtered, and evaporated to a sirup (0.35 g.) which was shown on a paper chromatogram to contain the required 6-*O*-isopropyl-D-glucose with R_{Rh} 1.7 contaminated with a little glucose. The glucose was removed by dissolution of the mixture in acetone and addition of a large excess of boiling ether. The liquid was decanted and evaporated to a small volume from which crystals (0.15 g.) were deposited. These were twice recrystallized from acetone to give material having m.p. 126–128° and $[\alpha]_D$ +90° → +50° (constant value; *c*, 0.5 H_2O).

Anal. Calcd. for $C_9H_{16}O_6$: C, 48.6%; H, 8.2%. Found: C, 48.8%; H, 8.2%.

6-O-Cyclohexyl-D-glucose. 3-*O*-benzyl-6-*O*-*p*-toluenesulfonyl-1,2-*O*-isopropylidene-D-glucofuranose (2.42 g.) was heated at 100° for 18 hr. in 50% cyclohexanol in dioxane (40 cc.) in which potassium (0.80 g.) had been dissolved. Benzene was added and the solution was extracted 3 times with water to remove salts. Evaporation yielded 3-*O*-benzyl-6-*O*-cyclohexyl-1,2-*O*-isopropylidene-D-glucofuranose (1.61 g.) as a brown sirup having $[\alpha]_D$ −18° (c, 1.4 MeOH).

The product (0.82 gm.) was hydrogenated, as with the isopropyl analog, to give sirupy colorless 6-*O*-cyclohexyl-1,2-*O*-isopropylidene-D-glucofuranose (0.52 gm.) with $[\alpha]_D$ −23° (*c*, 2.2 EtOH). Acid hydrolysis of the product followed by purification of the 6-*O*-cyclohexyl-D-glucose by ether extraction as in the preparation of 6-*O*-isopropyl-D-glucose furnished a solid (0.18 g.) which was recrystallized twice from acetone. The product softened at 105° and had m.p. 116–117° and $[\alpha]_D$ +66° → +37° (constant value; *c*, 0.7 H_2O).

(21) E. L. Hirst, D. I. McGilvray, and E. G. V. Percival, *J. Chem. Soc.*, 1297 (1950).

(22) W. Meijbaum, *Hoppe-Seyler's Z. physiol. Chem.*, 258, 117 (1939).

(23) A. S. Meyer and T. Reichstein, *Helv. Chim. Acta*, 29, 152 (1946).

Anal. Calcd. for $2C_{12}H_{22}O_6.H_2O$: C, 53.1%; H, 8.5%. Found: C, 53.0%; H, 8.7%.

Penta-O-acetyl 6-O-isopropyl-L-iditol. 1,2-3,4-Di-*O*-isopropylidene-L-iditol[24] (2.60 g.) was dissolved in pyridine (6 cc.) and *p*-toluenesulfonyl chloride (1.90 g.) in benzene (6 cc.) added.[25] After 3 hr., water (0.1 cc.) was added, followed by benzene and the reaction mixture was washed successively with dilute sulfuric acid, aqueous sodium bicarbonate, and then water. Evaporation of the benzene solution yielded 1,2-3,4-di-*O*-isopropylidene-6-*O*-*p*-toluenesulfonyl-L-iditol as a sirup (3.74 gm.) with $[\alpha]_D$ +1° (*c*, 2.2 EtOH).

The tosyl compound (0.94 g.) was heated for 18 hr. in refluxing isopropanol (30 cc.) in which sodium (0.20 g.) had been dissolved. Benzene was added and the solution was washed three times with water and then evaporated to a sirup (0.49 g.) with $[\alpha]_D$ +12° (c, 2.4 EtOH). Acid hydrolysis (30 min. at 100° in 5 cc. of 0.1*N* sulfuric acid) of the material which contained 6-*O*-isopropyl 1,2-3,4-di-*O*-isopropylidene-L-iditol yielded, after neutralization ($BaCO_3$), filtration, and evaporation, a complex mixture (0.32 g.). On a paper chromatogram, the main product had R_{Rh} 1.7 and components which moved at the speeds of rhamnose, ribose, and glucose.

The mixture (92 mg.) was acetylated in a manner identical to that used previously in the synthesis of tetra-*O*-acetyl-6-*O*-isopropyl-D-glucose. The sirupy product crystallized from ether-light petroleum (b.p. 30–60°) and two recrystallizations from the same solvent followed by one recrystallization from aqueous methanol yielded a product (49 mg.) with m.p. 87–88° and $[\alpha]_D$ −5° (c, 1.0 2,4-lutidine). Deacetylation yielded a polyol having R_{Rh} 1.7.

Anal. Calcd. for $C_{19}H_{30}O_{11}$: C, 52.5%; H, 7.0%. Found: C, 52.1%; H, 7.2%.

6-O-Cyclohexyl-L-iditol. 1,2-3,4-Di-*O*-isopropyl-6-*O*-*p*-toluenesulfonyl-L-iditol (8.0 g.) was mixed with a solution of dioxane (100 cc.) and cyclohexanol (100 cc.) in which potassium (3.0 g.) was dissolved. This was heated at 100° for 18 hr. and then evaporated as fully as possible. The solution was brought to neutrality with 6*N* hydrochloric acid and then acidified with 100 cc. of 0.1*N* hydrochloric acid in ethanol (200 cc.). The isopropylidene groups were removed from the 6-O-cyclohexyl-1,2-3,4-di-*O*-isopropylidene-L-iditol derivative by heating the solution under reflux for 2 hr. It was then neutralized (Ag_2CO_3), filtered, and evaporated to a mobile sirup to which water was added. Cyclohexanol was removed by shaking the liquid with light petroleum (b.p. 30–60°) and the remaining aqueous layer was evaporated to dryness. Extraction with hot acetone afforded a sirup (1.82 g.) which crystallized and was recrystallized twice from acetone-ether and then once from acetone. The product gave the properties expected of 6-*O*-cyclohexyl-L-iditol having m.p. 80–81°, $[\alpha]_D$ −7.5° (*c*, 1.0 sat. borax) and −2.5° (*c*, 1.0 H_2O), and consumed 4.1 moles/mole of sodium periodate with concomitant release of 2.9 moles/mole of formic acid.

Anal. Calcd. for $C_{12}H_{24}O_6$: C, 54.5%; H, 9.2%. Found: C, 54.5%; H, 9.0%.

Dihydro-D-altral from D-altrose. D-Altrose (22 g.) was converted to its pentaacetate by heating at 100° for 1 hr. in acetic anhydride (100 cc.) containing sodium acetate (10 g.). The reaction mixture was added, with stirring, to excess ice water and after 3 hr. the solution was extracted with benzene, which was washed 3 times with water, and evaporated to a sirup (27 g.).

The pentaacetate was dissolved in chloroform (250 cc.) and acetic acid saturated with hydrobromic acid (250 cc.) added. After 6 hr. at room temperature it was added with stirring to ice water and the chloroform layer was washed 4 times with water, dried ($MgSO_4$), filtered, and evaporated to a sirupy product (26 g.) which contained 2,3,4,6-tetra-*O*-acetyl-1-bromo-D-altrose.

The product was dissolved in acetic acid (60 cc.) and added to zinc dust (28 g.) contained in a vigorously stirred mixture of acetic acid (60 cc.) and water (120 cc.) cooled to −5°. The solution was allowed to warm to room temperature and after stirring overnight it was extracted with benzene, which was washed 3 times with water and evaporated to a sirup (4.1 g.).

Reduction of the 3,4,6-tri-*O*-acetyl-D-altral in methanol (25 cc.) containing platinic oxide (100 mg.) for 3 hr. at ambient pressure afforded a mixture to which sodium (100 mg.) was added in order to promote deacetylation. After 2 hr. the product was evaporated to a sirup (1.96 g.) which was fractionated on a cellulose column. A material (80 mg.) was obtained which, after two crystallizations from ethyl acetate, gave dihydro-D-altral, m.p. 105–106° and $[\alpha]_D$ +72° (*c*, 0.9 H_2O).

Anal. Calcd. for $C_6H_{12}O_4$: C, 48.6%; H, 8.2%. Found: C, 48.9%; 8.3%.

The material was identical, by its x-ray diffraction pattern and undepressed mixed melting point, with a dihydro hexital synthesized by von Rudloff and Tulloch.[9]

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SASKATOON, SASKATCHEWAN

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[CONTRIBUTION FROM THE SHELL DEVELOPMENT CO.]

Reactions of Hydrogen Peroxide. IV. Sodium Tungstate Catalyzed Epoxidation of α,β-Unsaturated Acids

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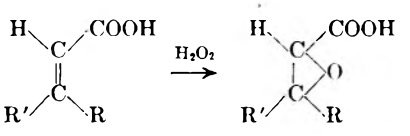
Maleic, fumaric, and crotonic acids, materials which are very resistant to attack by peroxyacetic and peroxybenzoic acids, have been efficiently converted to their corresponding epoxides in yields of 77, 50, and 50%, respectively, by means of hydrogen peroxide and sodium tungstate catalyst at *p*H 4–5.5.

The epoxidation of an α,β-unsaturated acid by the usual reagent such as peroxybenzoic or peroxyacetic acid is generally very slow; this is attributed to the electron-withdrawing effect of the carboxyl group directly attached to the ethylenic double bond.[1]

When higher temperatures are used in order to obtain practical reaction rates, hydroxylation rather than epoxidation is the end result.[2]

In the present work, maleic, fumaric, and crotonic acids were epoxidized with hydrogen peroxide by using sodium tungstate catalyst and maintaining the *p*H in the range 4–5.5. These acids had been *hydroxylated* earlier[3] by means of tungstic acid catalyst; however, no attempt was made in those cases to control the *p*H of the reaction so as to retard hydrolysis of the intermediate epoxide.



	Yield[4]
R = COOH, R′ = H,	77%
R = H, R′ = COOH,	50%
R = H, R′ = CH_3	50%

Maleic acid reacted extremely rapidly with hydrogen peroxide and 2 mole % of catalyst, only 1.5 hr. being required for complete reaction at 65°. Disodium *cis*-epoxysuccinate was obtained in quantitative yield and was 95% pure by titration for oxirane oxygen. The free acid was best prepared from the barium salt by means of ethereal sulfuric acid[5a]; use of the sodium salt led to considerably lower recoveries of pure acid. *cis*-Epoxysuccinic acid has been prepared before, by the chlorohydrination route[3] as well as by the action of alkaline hydrogen peroxide on hydroquinone or *p*-benzoquinone.[6]

Fumaric acid, with only 2 mole % of catalyst, was epoxidized to the extent of only 25% after 1.5 hr. at 65°; continued reaction resulted in a substantial amount of epoxide hydrolysis. In order to obtain a practical rate of epoxidation, it was necessary to employ 10 mole % of catalyst; there was then obtained a crude disodium *trans*-epoxysuccinate (heavily contaminated with sodium tungstate) which, by titration for oxirane oxygen, contained epoxy product in an amount corresponding to a yield of 86%. The free epoxy acid was again secured by treatment of its barium salt with sulfuric acid in ether. *Trans*-epoxysuccinic acid has been prepared before *via* the chlorohydrination of fumaric acid.[5]

Crotonic acid reacted somewhat more readily than fumaric; however, 10 mole % of catalyst was again required in order to limit the reaction time and moderate hydration of the epoxide linkage. The yield of epoxide by titration of the reaction mixture was 80%; however, difficulty was encountered in isolating free acid and the yield of material having a purity of 87% was 57%. Essentially pure 2,3-epoxybutyric acid was obtained in 30% yield based on crotonic acid charged. This epoxy acid has been prepared earlier by allowing crotonic acid to react with peroxybenzoic acid for three months,[7] *via* hypochlorination of crotonic acid,[7] and by the hypobromite oxidation of crotonaldehyde.[8a]

This epoxidation procedure has also been applied to materials other than α,β-unsaturated acids and with particular success to allylic alcohols.[8b] Simple olefinic compounds, however, have been found to be of lesser reactivity. For example, 2-heptene, a compound that is readily attacked by organic peroxyacids,[1] underwent only 66% re-

(1) D. Swern, *J. Am. Chem. Soc.*, **69**, 1692 (1947).

(2) G. S. Myers, *J. Am. Chem. Soc.*, **73**, 2100 (1951); J. English, Jr., and J. D. Gregory, *J. Am. Chem. Soc.*, **69**, 2120 (1947).

(3) M. Mugdan and D. P. Young, *J. Chem. Soc.*, 2988 (1949); J. M. Church and R. Blumberg, *Ind. Eng. Chem.*, **43**, 1780 (1951); R. P. Linstead, L. N. Owen, and R. F. Webb, *J. Chem. Soc.* 1218 (1953).

(4) Yields of purified acids; the yields of sodium salts were 95, 86, and 80%, respectively, calculated from titration for oxirane oxygen.

(5) (a) R. Kuhn and F. Ebel, *Ber.*, **58B**, 919 (1925); (b) Y. Inoue, M. Hamada, and S. Asano, *J. Agr. Chem. Soc. Japan*, **19**, 17 (1943); *Chem. Abstr.*, **45**, 8980, (1951); (c) J. Timmermans, P. Machtelinckx, and J. Mokry, *Bull. chim. soc. Belg.*, **60**, 424 (1951).

(6) E. Weitz, H. Schobbert, and H. Seibert, *Ber.*, **68B**, 1163 (1935).

(7) G. Braun, *J. Am. Chem. Soc.*, **52**, 3185 (1930).

(8)(a) A. A. Kaufmann, U. S. Patent **1,858,551** (May 17, 1932). (b) G. J. Carlson, J. R. Skinner, C. W. Smith, and C. H. Wilcoxen, Jr., (to Shell Development Co.) U.S. Patent **2,833,787**(May 6, 1958).

action in 6 hr. at 65° (10 mole % of catalyst) to give (by titration for oxirane oxygen) a 55% yield of epoxide based on hydrogen peroxide reacted. There was also observed a considerable loss of peroxide due to decomposition during the lengthy reaction period.

It is possible, indeed probable, that the relatively high reactivity of α,β-unsaturated acids is due to the formation of an intermediate cyclic complex involving substrate and inorganic peroxyacid. The elucidation of this reaction mechanism is the subject of a continuing study.

EXPERIMENTAL[9]

Disodium cis-epoxysuccinate. To a 1-liter, 5-neck, round-bottom flask equipped with stirrer, thermometer, and dropping funnel was charged a filtered solution of 116 g. (1.0 mole) of maleic acid (E. K. Co.) in 300 ml. of distilled water. To this was added a solution of 60 g. (1.5 moles) of sodium hydroxide in 100 ml. of water. The heat of neutralization caused a rise in temperature to about 70°. To the warm solution was added 6.6 g. (0.02 mole) of sodium tungstate dihydrate (Baker and Adamson). Standard *p*H electrodes were inserted into the solution and 1.2 mole of 30% hydrogen peroxide was added in one portion.[10] The strongly exothermic reaction was held at 63–65° by cooling with an ice bath for about 15 min. during which time the *p*H fell from about 5.5 to 4.[11] In order to maintain the *p*H at a minimum of 4, a solution of 0.5 mole of sodium hydroxide in 100 ml. of water was added dropwise as needed throughout the remainder of the reaction. After an additional hour at 65°, iodometric titration indicated the consumption of 1.02 moles of hydrogen peroxide, and the solution was cooled to 40° and treated with the remainder of the sodium hydroxide solution. After vacuum concentration[12] at 40° to a volume of about 300 ml., the residual liquid was poured with stirring into 1.5 liters of acetone to precipitate 176 g. (100%) of disodium *cis*-epoxysuccinate.

Anal. Calcd. for $C_4H_2O_5Na_2$: oxirane oxygen, 9.1. Found: oxirane oxygen, 8.6.[13]

The *barium salt* was prepared from sodium salt by the addition of a solution of the latter to a molar equivalent of barium chloride dissolved in hot water (33 g. per 100 ml.). The recovery of barium *cis*-epoxysuccinate dihydrate was essentially quantitative.

Anal. Calcd. for $C_4H_2O_5Ba\cdot 2H_2O$: C, 15.8; H, 2.0. Found: C, 15.3; H, 2.1.

cis-Epoxysuccinic acid. The procedure employed was a modification of that used by Kuhn and Ebel.[5a] A suspension of 152 g. (0.50 mole) of barium salt and 30 g. of anhydrous magnesium sulfate in 750 ml. of ether was stirred at 0–5° and treated dropwise over 1 hr. with a solution of 49 g. of sulfuric acid in 200 ml. of ether. After an additional hour at 5–10°, the mixture was allowed to stir overnight at room temperature. After removal of barium sulfate by filtration, the filtrate was dried over magnesium sulfate and concentrated under vacuum to a constant weight of 51 g. (77%), m.p. 148–149°; reported[5a] m.p. 149°.

Anal. Calcd. for $C_4H_4O_5$: Neut. equiv., 66.0; oxirane oxygen, 12.1 Found: Neut. equiv., 66.4; oxirane oxygen, 11.7.[13]

Epoxidation of fumaric acid. The epoxidation was carried out essentially as above (E. K. Co. fumaric acid, recrystallized from water) except for the use of 10 mole % of sodium tungstate instead of 2 mole %. After 3 hr. at 65° and 1 hr. at 75–80°, the solution was processed as above to yield 222 g. of a mixture containing sodium tungstate and 0.86 mole of disodium *trans*-epoxysuccinate (titration for oxirane oxygen[13]). The *barium salt* was prepared as above, 108 g. being obtained from 84 g. of crude sodium salt. The 108 g. was suspended in 500 ml. of ether containing 5 ml. of water and treated as above with a solution of 37 g. of sulfuric acid in 100 ml. of ether. After stirring overnight, the salt was removed by filtration and the filtrate concentrated to a volume of about 200 ml. and diluted with two volumes of petroleum ether (40–60°). The solid product thus obtained was collected by filtration and washed with more petroleum ether. An additional amount was secured by again stirring the recovered barium sulfate overnight with 500 ml. of ether and repeating the isolation procedure. The combined weight of epoxy acid thus obtained was 30 g. (60% yield based on fumaric acid) m.p. 207–209°; reported m.p. 209°[5a] and 208–209°.[5b]

Anal. Calcd. for $C_4H_4O_5$: Neut. equiv., 66.0; oxirane oxygen, 12.1. Found: Neut. equiv., 65.2; oxirane oxygen, 9.5.[13]

In view of the low value for oxirane oxygen, a 5.8-g. sample was heated in 50 ml. of water to 80°, cooled to room temperature, and filtered to remove 0.9 g. of insoluble solid (probably crude fumaric acid). Concentration of the filtrate afforded 4.9 g. of purified *trans*-epoxysuccinic acid, *instantaneous* m.p. 233° (reported[5c] *instantaneous* m.p. 232°), neut. equiv., 66.0; oxirane oxygen, 11.1.[13]

2,3-Epoxybutyric acid. One mole (86 g.) of crotonic acid (E. K. Co., recrystallized, m.p. 71–72°) was added to a solution of 20 g. (0.50 mole) of sodium hydroxide in 250 ml. of water. This solution was filtered into a 1-liter flask equipped as above, warmed to 55°, and treated with 33 g. (0.10 mole) of sodium tungstate dihydrate. To the stirred mixture, 1.30 moles of 30% hydrogen peroxide was added dropwise over 5 min. The reaction temperature was held at 63–65° by cooling and the *p*H held above 4 by dropwise addition of 30% alkali as needed. After 1 hr. at the same temperature, the mixture was cooled and titrated for oxirane oxygen;[13] a yield of 80% was indicated. Sulfuric acid (30%) was added dropwise to a *p*H of 2.5 and the epoxy acid was isolated by saturating with ammonium sulfate, extracting with five 200-ml. portions of ether and drying over magnesium sulfate. After removal of the ether *in vacuo* there remained 58 g. (50% yield allowing for purity) of crystalline epoxy acid; the purity was 87% by titration for oxirane oxygen.[13] A 50-g. sample, on recrystallization from 150 ml. of benzene, gave 26 g. of purified 2,3-epoxybutyric acid, m.p. 84.5–85°; reported m.p. 88.5°[7] and 84°.[8]

Anal. Calcd. for $C_4H_6O_3$: Neut. equiv., 102; oxirane oxygen, 15.7. Found: Neut. equiv., 103; oxirane oxygen, 15.1.[13]

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(9) All melting points are corrected.

(10) In larger scale runs the peroxide was added dropwise over 0.3–0.5 hr.

(11) The drop in *p*H can be attributed to the formation of a considerably stronger acid: pK_2 for *cis*-epoxysuccinic acid is 3.92 as against pK_2 of 6.5 for maleic acid; *Cf.* A. Wasserman, *Helv. Chim. Acta*, **13**, 207 (1930).

(12) A circulating evaporator was used; see *Ind. Eng. Chem., Anal. Ed.*, **16**, 754 (1944).

(13) A sample was allowed to stand overnight in 0.1*N* hydrochloric acid saturated with magnesium chloride; the mixture was back-titrated with 0.1*N* sodium hydroxide to the bromcresol purple end point.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, CASE INSTITUTE OF TECHNOLOGY]

Cation Exchange Resin-Catalyzed Condensation and Polymerization of Aldehydes and Cyclohexanone

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A study was made of the use of strongly acid cation exchange resins to catalyze the self-condensation and polymerization of aliphatic aldehydes and cyclohexanone. Of 10 aldehydes tested, only those of lower molecular weight gave appreciable yields of pure compounds. Near or below room temperature, propionaldehyde, *n*-butyraldehyde, and isobutyraldehyde, gave para-aldehydes. At reflux, propionaldehyde, *n*-butyraldehyde, isovaleraldehyde, and *n*-caproaldehyde were converted to dialkyl acroleins. Isobutyraldehyde was converted to the alkyl hydroxytrioxane. Cyclohexanone yielded cyclohexenylcyclohexanone. The addition of water or solvent hindered the catalysis, but re-use of the catalyst had little effect if water of hydration was removed. Approximately maximum conversion was achieved in one hour by the use of 25% Amberlite IR-120 or Dowex 50, based on the weight of aldehyde. All runs at reflux produced a distillation residue which is suggested to be a linear polymer based on a polyoxymethylene chain.

The purpose of the present investigation was to extend the work of Durr and co-workers[1-3] on the self-condensation of aliphatic aldehydes and cyclohexanone in the presence of strongly acid cation exchange resins. Durr reported the formation of dialkylacroleins from the 4-, 6-, and 7-carbon atom normal aliphatic aldehydes, and cyclohexylidenecyclohexanone from cyclohexanone, in the presence of Amberlite IR-120 at 130° to 150°, generally above the normal reflux temperature of the carbonyl compounds. At ambient temperature he obtained no product from *n*-butyraldehyde or *n*-heptaldehyde, but obtained paraldehyde from acetaldehyde. He also studied the effect of some reaction conditions on the crotonization of *n*-heptaldehyde.

In the present investigation, an extensive study has been made of the effect of the following variables on the polymerization and self-condensation of *n*-butyraldehyde: (a) reaction temperature from about 30° to 80°, (b) reaction time from 0.5 to 12 hr., (c) quantity of catalyst from 5 to 25% of the weight of the aldehyde, (d) brand of cation resin (Amberlite IR-120 and Dowex 50), (e) repeated reuse of the catalyst, (f) addition of a nonreactive solvent, and (g) addition of a small quantity of water.

With the results of this study as a background, nine other aldehydes and cyclohexanone were treated with one of the resins. A hypothesis is offered to explain the relative reactivity of some of the aldehydes and to indicate a possible structure of the distillation residues which were obtained.

EXPERIMENTAL

Preparation of materials. Cation exchange resins. The resins as received were treated with about 500 ml. of 7–9% hydrochloric acid per 100 grams, washed free of acid and chloride, rinsed with acetone, air dried, and finally vacuum dried at 60–65°.

Carbonyl compounds. All these compounds were dried, distilled, stored under nitrogen in dark bottles, and used within 10 days after distillation. Their boiling points and refractive indices compared favorably with those reported in the literature.

The condensations were all carried out in essentially the same way.

The carbonyl compound and the ion exchange resin were agitated in a flask equipped with condenser, nitrogen bubbler, magnetic stirrer, and as the occasion required, a Dean-Stark water trap. Heating or cooling was provided as needed. At the end of the reaction period, the ion exchange resin was removed by filtration, and the filtrate, which was free of suspended matter, was fractionally distilled. Refractive indices and infrared spectra were taken of the fractions, and other physical and chemical properties were determined as aids to identification. Molecular weights were determined cryoscopically in benzophenone. When the product was believed to be a substituted trioxane, confirmation was sought by heating it with a trace of *p*-xylene–2-sulfonic acid, distilling, and identifying the original aldehyde, which would be regenerated by this procedure.

If the same portion of ion exchange resin was to be used again, it was washed with benzene or acetone until the air-dried resin was substantially odorless.

Condensation of n-butyraldehyde. *n*-Butyraldehyde (100 g.) containing 25 g. of Amberlite IR-120 was stirred at the desired temperature. At the end of the run the ion exchange resin was removed by filtration and the filtrate fractionated.

The results of triplicate experiments carried out at reflux temperatures agreed within 10%. The relative proportions of products showed little variation.

Condensation of other aldehydes. The self-condensation of 9 other aldehydes was accomplished in the same way. When it was desirable to remove the water of reaction as formed, a Dean-Stark water trap was used.

Condensation of cyclohexanone. Cyclohexanone was condensed by refluxing with Dowex 50 × 8 at 106–115°. A 23% conversion was obtained in 1 hr.

Infrared analysis. All infrared absorption curves were obtained using a Perkin-Elmer Infracord.

DISCUSSION

The product obtained by the condensation of butyraldehyde together with their properties are listed in Table I, and the effects of various reaction conditions are shown in Table II.

(1) G. Durr, *Compt. rend.*, **237**, 1012 (1953).
(2) G. Durr, *Ann. Chem.*, [13] **1**, 84 (1956).
(3) P. Mastagli and G. Durr, *Bull. soc. chim. France*, 268 (1955).

TABLE I

REACTION DATA AND DESCRIPTION OF PRODUCTS

Starting Material	Reaction Conditions	Conversion, %	Product	Properties of Product: Boiling Range °C.	Boiling Range Mm.	Refractive Index n_D^{20}	Weight, Molecular Found
Propionaldehyde	Reflux 6 hr., 50–62°	>41	2-Methyl-3-ethylacrolein	28	8	1.4491	
	Reflux 6 hr., 50–62°	18	Distillation residue			1.4770	260
	Stir 3 hr., −31–0°	75	Parapropionaldehyde	45–50	2.2–4.7	1.4170	180
Crotonaldehyde	Reflux 1 hr., 94°	14	Distillation residue				
n-Butyraldehyde	Reflux 1 hr., 68–73°	62	2-Ethyl-3-propylacrolein	42–45	1.8–2.0	1.4528	
n-Butyraldehyde	Stir 1 hr., 27–31°	48	Parabutyraldehyde	77–85	3	1.4261	210
	Reflux 6 hr., 73–87°	16	Distillation residue				
Isobutyraldehyde	Reflux 6 hr., 62–65°	33	5,5-Dimethyl-2,4-diisopropyl-6-hydroxy-1,3-dioxane	102	3	1.4438	226
	Reflux 6 hr., 60–63°	27	Distillation residue			1.4621	>380
	Stir 50 min., 27–45°	91	Paraisobutyraldehyde	58.1–58.9 (m.p.)			210
Isovaleraldehyde	Reflux 1 hr., 90–91°	22	2-Isopropyl-3-isobutylacrolein	45–50	2–3	1.4459	
		9	Distillation residue			1.4508	>270
2-Methylvaleraldehyde	30 g., Stir 80 min., 1–20°	4	Distillation residue				
2-Ethylbutyraldehyde	Reflux 3 hr., 104–119°	41	Distillation residue			1.502	
n-Caproaldehyde	Reflux 1 hr., 105–109°	9	2-Butyl-3-amylacrolein	68–93	2	1.4519	
		21	Distillation residue			1.515	
2-Ethylcaprohyde	Reflux 6 hr., 136–150°	60	Distillation residue			1.497	540
Benzaldehyde	Stir 30 min., 25°	0	No reaction				
Cyclohexanone	Reflux 1 hr., 106–115°	23	1-Cyclohexenyl-2-cyclohexanone	114–8	3	1.5070	184
	Reflux 5 hr.,	100	Resinous polymer				
Cyclohexanone *n*-Butyralde-	0.6 Mole each Reflux 2 hr., 78–91°	20	2-Cyclohexylidenebutyraldehyde	68–78	2	1.4798	
		23	Distillation residue				
	0.6 Mole each Stir 3 hr., 30–33°	9	Not identified	71	1.8	1.4690	

Effect of reaction temperature. The product which was formed depended on the reaction temperature. In addition to a distillation residue which was obtained in all runs, refluxing for 1 hr. at 73–80° converted 62% of the butyraldehyde to 2-ethyl-3-propylacrolein, in agreement with Durr's finding.[2] On the other hand, stirring for 1 hr. at 27–31° converted 48% of the butyraldehyde to parabutyraldehyde (2,4,6-tripropyl-1,3,5-trioxane) and only 1% to ethylpropylacrolein. At a little higher temperature, 33–45°, a little more dialkylacrolein and a little less parabutyraldehyde were formed.

Effect of reaction time. Refluxing for more than 1 hr. had only a minor effect on the over-all conversion, but increased the amount of distillation residue a little at the expense of the ethylpropylacrolein. Stirring for 1 hr. at about 25–45° gave somewhat more parabutyraldehyde and ethylpropylacrolein than did stirring for only 30 min. The formation of a product at ambient temperature is in contrast to Durr's report that butyraldehyde underwent no reaction in the presence of Amberlite IR-120 at this temperature.[2]

Effect of quantity of catalyst. The use of 5 or 10 g. instead of 25 g. Amberlite IR-120 per 100 g. butyraldehyde decreased the conversion to substituted acrolein by 18–34% during 6 hr. reflux. The quantity of residue formed was fairly constant. This result disagrees with Durr's report that the effect of increasing the quantity of catalyst had

TABLE II

EFFECT OF REACTION CONDITIONS ON PRODUCTS OBTAINED FROM *n*-BUTYRALDEHYDE

Reaction Conditions	Percent Conversion to: 2-Ethyl-3-propyl acrolein	Para-butyral-dehyde	Distil-lation residue	Total
Effect of Reaction Temperature				
Refluxed 1 hr., 73° to 80°	62	0	7	69
Stirred 1 hr., 33° to 45°	8	32	6	46
Stirred 1 hr., 27° to 31°	1	48	9	58
Effect of Reaction Time				
Refluxed 1 hr., 73° to 80°	62	0	7	69
Refluxed 6 hr., 73° to 87°	61	0	14	75
Refluxed 12 hr., 71° to 112°	54	0	19	73
Stirred 30 min., 25° to 43°	1	28	6	35
Stirred 1 hr., 33° to 45°	8	32	9	49
Effect of Re-use of Catalyst				
1st use; 1 hr. at 73° to 81°	62	0	7	69
2nd use; 1 hr. at 74° to 81°	50	0	15	65
4th use; 1 hr. at 67° to 69°	24[d]	0	10	34
5th use; 1 hr. at 67° to 72°	22	0	20	42
6th use; 1 hr. at 69° to 72°	41	0	23	64
7th use; 1 hr. at 68° to 69°	21	0	22	43
8th use; vacuum dried; 1 hr. at 68° to 75°	50	0	18	68
1st use, stirred 1 hr. at 25° to 41°	8	32	8	48
3rd use, stirred 1 hr. at 25° to 45°	6	22	26	54

Reaction Conditions	Percent Conversion to: 2-Ethyl-3-propyl acrolein	Para-butyral-dehyde	Distil-lation residue	Total
Effect of Quantity of Catalyst at Reflux				
5g IR-120; 6 hr., 73° to 76°	27[a]	0	22	49
10g IR-120; 6 hr., 74° to 84°	43	0	15	58
25g IR-120; 6 hr., 73° to 80°	61	0	14	75
Effect of Inert Solvent at Reflux				
1 hr., 73°; 1:1 aldehyde: benzene	29[b]	0	5	34
1 hr., 73° to 80° no solvent	62	0	7	69
6 hr., 73°; 1:1 aldehyde: benzene	46[c]	0	14	60
6 hr., 73° to 87° no solvent	61	0	14	75
Effect of Added Water at Reflux				
1 hr., 65° to 67° 10 ml. water	6	0	3	9
1 hr., 67°; 10 ml water	13	0	11	24
1 hr., 69° to 73°; same resin vacuum dried at 70°	50	0	22	72
1 hr., 73° to 80°; no water	62	0	7	69
Comparison between Dowex 50 and Amberlite IR-120				
Dowex; reflux 1 hr., 71° to 78°	47	0	18	65
Amberlite; reflux 1 hr., 73° to 81°	62	0	7	69
Dowex; reflux 6 hr., 69° to 86°	65	0	15	80
Amberlite; reflux 6 hr., 73° to 87°	61	0	14	75
Dowex; stir 1 hr., 27° to 30°	9	57	13	79
Amberlite; stir 1 hr., 27° to 31°	1	48	9	58

[a] Including 3% of a mixed product. [b] Including 11% of a mixed product. [c] Including 3% of a mixed product. [d] Including 9% of a mixed product.

little effect above 5–10 g. of IR-120 per 100 g. *n*-heptaldehyde reacting at 145–150° for 2 hr.[2] However, the higher reaction temperature and higher molecular weight of the aldehyde he used may explain the difference.

Effect of inert solvent. Dilution of the butyraldehyde with an equal weight of benzene decreased the conversion to ethylpropylacrolein but had little effect on the quantity of distillation residue.

Effect of added water. The data for two runs show that the addition of 10 ml. deionized water prior to refluxing markedly decreased the conversion to substituted acrolein. When the resin catalyst from one of these runs was re-used after being vacuum dried, its catalytic activity was substantially restored. Evidently the water interfered with the catalysis, possibly by being adsorbed at the active sites on the resin surface or by clogging the pores in the particles.

Effect of re-use of the catalyst. When the same portion of Amberlite IR-120 was shaken for 1 hr. with each of three successive portions of butyraldehyde at 25–45°, the over-all conversion was similar in each run, although the relative proportions of prod-

ucts showed some variation. A parallel series of runs in which the same resin was used seven times under reflux at 67–81° gave a different result. There was about a 30% decrease in total conversion and about a 60% decrease in ethylpropylacrolein. Just before the same portion of resin was used for the eighth time it was heated for 4.5 hr. at 65° under 50-mm. pressure, whereupon its catalytic activity was restored substantially to the original level. Since this result was analogous to the deactivation of the resin by the deliberate addition of water and its reactivation by drying, the loss of activity during re-use was probably the result of the adsorption of water which was produced together with ethylpropylacrolein. For the same reason, reuse of the catalyst at lower temperatures caused no deactivation because much less of the acrolein was formed.

Comparison of Amberlite IR-120 with Dowex 50 × 8. Although these resins have similar chemical structures and exchange capacities, Dowex appeared to have greater catalytic activity. The two resins gave similar results under reflux, but Dowex gave more parabutyraldehyde when stirred at 27–30°. These differences may be attributable to the smaller particle size and hence the greater specific surface of the Dowex. Accordingly, Dowex was used preferentially in experiments with other aldehydes, as described below.

Reactions of other aldehydes. The self-condensation was studied with nine other aldehydes; three with two hydrogen atoms on the alpha carbon atom (propionaldehyde, isovaleraldehyde, *n*-caproaldehyde), five with only one alpha hydrogen atom (crotonaldehyde, isobutyraldehyde, 2-methylvaleraldehyde, 2-ethylbutyraldehyde, 2-ethylcaproaldehyde), and benzaldehyde. Unless otherwise indicated, the catalyst was Dowex 50. The products and their properties are listed in Table I.

Reactions near or below room temperature. The only products formed near or below room temperature were the cyclic trimers (paraaldehydes) of propionaldehyde and isobutyraldehyde. Of the other aldehydes, only isovaleraldehyde has been reported to form the cyclic trimer.[4] In no case was any meta-aldehyde detected. The conversion to parapropionaldehyde was better at −31–0° (75%) than at 27–45° while a temperature of 23–30° was more favorable for the formation of paraisobutyraldehyde (91% conversion) than was −13° to −4°.

Reactions at reflux. All three of the aldehydes with two hydrogen atoms on the alpha carbon atom yielded dialkyl acroleins, but only the two of lower molecular weight underwent substantial conversion. This trend differs from Durr's finding that as much as 71% of *n*-heptaldehyde was converted to the acrolein, but his reaction temperature was higher (150°).

Propionaldehyde refluxed for 6 hr. at 50–62° gave a 41% yield of 2-methyl-3-ethylacrolein and 18% distillation residue. Refluxing for 1 hr. at 90–91° converted 22% of isovaleraldehyde to 2-isopropyl-3-isobutylacrolein, while 1 hr. at 105–109° converted only 9% of the caproaldehyde to 2-butyl-3-amylacrolein. The conversions to residue were 9 and 21%, respectively. Attempts were made to approach Durr's higher conversions of caproaldehyde by continuously removing water of reaction so as to raise the reaction temperature to 155°, and by substituting Amberlite IR-120 for Dowex 50, but the only result was less of the substituted acrolein (4 and 0%) and more of the distillation residue (54 and 34%).

Of three aldehydes with one alkyl group on the alpha carbon which were refluxed with Dowex 50 for 1 to 6 hr., only isobutyraldehyde was extensively converted (33%) to a distillable product. The product appeared to be 5,5-dimethyl-2,4-diisopropyl-6-hydroxydioxane contaminated with a minor quantity of isobutyraldol which could not be removed even upon redistillation. Saunders[5] has similarly found that this alkylhydroxydioxane tends to dissociate to the aldol during vacuum distillation. About 25% of the isobutyraldehyde was converted to distillation residue and 5–10% to paraisobutyraldehyde. Refluxing isobutyraldehyde always gave some paraisobutyraldehyde, and when the reflux reaction was carried out for only 1 hr., the conversion to par-aldehyde was almost 20%.

Refluxing 2-ethylbutyraldehyde at 107° or 2-ethylcaproaldehyde at 109° for 1 hr. gave no distillable product and only 6–7 % distillation residue. Forcing the reaction by refluxing for 3 to 6 hr. and continuously removing water so that the reaction temperature rose to 155° resulted in 60% conversion to distillation residue but only 4–6% conversion to distillable material which was probably a product of decomposition. It thus appears that of all the aldehydes tested, only those of low molecular weight were significantly converted to simple products. This is consistent with Haskell and Hammett's finding that the relative rate constant for the cationic resin-catalyzed hydrolysis of esters decreased tenfold from methyl acetate to ethyl caproate.[6]

Condensation of cyclohexanone. The properties of the products obtained from the condensation of cyclohexanone are listed in Table I. Durr[7] working with Amberlite IR-120 and Dietrich[8] working with a resorcinol-formaldehyde sulfonic acid resin, reported the product to be 1-cyclohexylidene-2-cyclohexanone. However, the following evidence indi-

(4) A. Franke and H. Wozelka, *Monatsh.*, **33**, 349 (1912).

(5) R. H. Saunders, M. J. Murray, and F. F. Cleveland, *J. Am. Chem. Soc.*, **65**, 1714 (1943).

(6) V. C. Haskell and L. P. Hammett, *J. Am. Chem. Soc.*, **71**, 1284 (1949).

(7) G. Durr, *Compt. rend.*, **236**, 1571 (1953).

(8) W. Dietrich, German Patent **857,960**, Dec. 4, 1952; *Chem. Abstr.*, **47**, 11240 (1953).

cates the product to be cyclohexenylcyclohexanone:

(1) The infrared spectrum indicated the carbonyl group was not conjugated to the carbon-carbon double bond.

(2) The melting point of the 2,4-dinitrophenylhydrazone (154.6° to 155.0°) agreed with that published for this derivative of cyclohexenyl cyclohexanone,[9] not with 129° to 130° published for the derivative of cyclohexylidenecyclohexanone.[10]

(3) The molar refraction, 52.8, indicated there was no exaltation, as would be expected from the conjugated system in cyclohexylidenecyclohexanone.

These observations have recently been confirmed by Lorette.[11]

The wide range and similarity of the boiling ranges, refractive indices, and densities of the two compounds preclude their use in identification, and the melting points of the oxime and semicarbazone of cyclohexenylcyclohexanone have not been reported.

When cyclohexanone was refluxed with Dowex 50 for 5 hr. at 113° to 169° and water was continuously removed, it was almost completely converted to a thermoplastic semisolid resinous material.

When 0.6 mole butyraldehyde was refluxed with 0.6 mole cyclohexanone and the catalyst for 1 hr., about 23% was converted to what was probably 2-cyclohexylidenebutyraldenyde (properties listed in Table I). Lambert, Durr, and Millet[12] carried out a similar reaction, and called their product 2-cyclohexylidenebutyraldehyde. The two products had very similar boiling ranges and refractive indices, and the 2,4-dinitrophenyl hydrazones had like melting points. In addition, the infrared spectrum was appropriate. A similar procedure with butyraldehyde and cyclohexanone, but carried out at 30–33°, converted a few percent of the butyraldehyde to ethylpropylacrolein and about 9% to an unsaturated product which was not satisfactorily identified. The molecular weight, 153, corresponded to the dehydrated product of one mole each of aldehyde and ketone, but the infrared spectrum indicated that the compound was not the same as the one previously described as cyclohexylidene butyraldehyde.

Distillation residues. Examination of the infrared spectra of the distillation residues from the self-condensation of all the aldehydes tested indicated that all the residues contained —C—O—C—O—C— and unconjugated carbonyl groups. In addition, the residues from the aldehydes with two hydrogen atoms on the alpha carbon atom also contained conjugated carbonyl and carbon-carbon double bonds. The residues were viscous, thermoplastic materials whose molecular weights (Table I) corresponded to 3 to 7 moles of aldehyde, depending on how much allowance was made for loss of water of dehydration. This information suggests that the residues were linear polymers based on a —C—O—C—O—C— chain analogous to that proposed by Staudinger[13] for certain acetaldehyde polymers and that the mechanism of their formation is independent of any aldolization reaction. The carbonyl and carbon-carbon double bonds would then be located in groups attached to the main chain, indicating that some of the side groups were at least dimers of the original aldehydes. Since the distillable, linear products which have been discussed previously were dimers or dehydrated dimers, it might be expected that the side groups were mostly formed first and the polymer chain afterward. It may be significant that, unlike the cyclic trimers which also contain the —C—O—C—O—C— structure, the residues did not yield the original carbonyl compound when heated with acid. According to the foregoing theory, even if the chain were hydrolyzed, the hydrolyzate would consist of dimers or higher polymers (dehydrated in some cases) of the original compound. A relatively high temperature would be required to distill them, and if liberated slowly they would probably form new —C—O—C—O—C— chains as fast as the old ones were broken in the presence of the acid catalyst.

CLEVELAND, OHIO

(9) A. S. Dreiding and R. J. Pratt, *J. Am. Chem. Soc.*, **75**, 3717 (1953).

(10) D. D. Venus, *et al.*, *J. Gen. Chem. U.S.S.R. (Eng. Transl.)*, **23**, 1561 (1953).

(11) N. B. Lorette, *J. Org. Chem.*, **22**, 346 (1957).

(12) P. Lambert, G. Durr, and G. Millet, *Compt. rend.*, 251 (1954).

(13) A. Staudinger, *Trans. Faraday Soc.*, **32**, 250 (1936).

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, RESEARCH AND ENGINEERING DIVISION, MONSANTO CHEMICAL CO.]

Reductive Acetylation of Diene-Haloquinone Adducts

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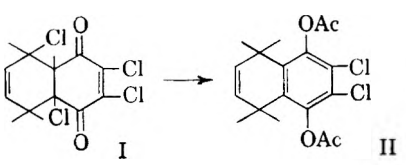
Adducts from chloranil or 2,5-dichloroquinone with simple dienes were converted in high yields to 2-chloro- or 2,3-dichloro-5,8-dihydro-1,4-diacetoxynaphthalenes by zinc in acetic anhydride in the presence of tertiary amines. Tetrahydro and aromatic derivatives were prepared from the dihydro diacetates. Catalysis of the isomerization-acetylation of quinone-diene adducts by tertiary amines and the acid-catalyzed reaction with isopropenyl acetate are described.

An earlier paper[1] described adducts (I) obtained from dienes and chloranil or dichloroquinones and methods for the selective reductive removal of the angular chlorines to obtain 2-chloro- or 2,3-dichloro-5,8-dihydro-1,4-naphthohydroquinones. Certain disadvantages were apparent in the latter intermediates: they were sensitive to light and air and could not be handled conveniently; although the naphthoquinones could be obtained from them by oxidation *in situ* in 51–85% yields, aromatic hydroquinone derivatives were available only after several laborious steps with further reduction in yield. In addition, derivatives with lower phytotoxicities than either the hydroquinones or quinones[2] were desired for projected biological applications. This paper describes useful direct syntheses for dihydro hydroquinone diacetates which have more tractable properties and are useful intermediates.

The use[1] of the zinc–acetic acid couple and similar reducing agents with diene-haloquinone adducts (I) was formally analogous to the usual methods for reducing quinones to hydroquinones. To obtain the corresponding diacetates it seemed reasonable to apply a procedure, termed "reductive acetylation," for the conversion of quinones to hydroquinone diacetates, involving zinc dust in acetic anhydride with pyridine as a catalyst.[3]

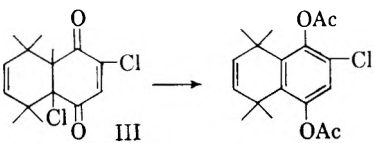
When I was treated in this manner, a much more vigorous exothermic reaction occurred than is given by quinones. The rather pure dihydro diacetate (II) was isolated in essentially quantitative yield. The reaction was extended to adducts from isoprene, 2,3-dimethylbutadiene, 2-methyl-1,3-pentadiene, and cyclopentadiene to give 6-methyl-, 5,7-, and 6,7-dimethyl-, and 5,8-methylene-derivatives of II in 74–98% yields.



I II

The structure was confirmed by hydrogenation to a tetrahydro derivative and by oxidation to the known aromatic diacetate. The oxidation of these materials with chromic acid was much superior to the use of sulfur at 230–240°. For most of these compounds, the reactions of this paper are the synthetic methods of choice.

The method was also applied successfully to adducts (III) from 2,5-dichloroquinone in 84–88% yields. In this case sulfur was used effectively in the dehydrogenation to an aromatic diacetate.



III

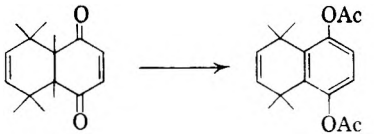
The function of the catalyst was investigated briefly. The cyclopentadiene-chloranil adduct (which is somewhat more labile than the adducts derived from butadienes) gave an infusible black powder and no dihydro diacetate when slowly warmed with zinc dust in acetic anhydride without pyridine. However, other tertiary amines (dimethylaniline and tri-*n*-hexylamine) could be substituted for pyridine without affecting the yield. In other reactions to which pyridine was not added until the mixture had been heated to 50–60°, it was noted that the zinc dust became agglomerated and that these aggregates were destroyed by pyridine, suggesting that reaction occurred on the surface of the zinc, coating it with the zinc salt of the hydroquinone, which did not react with acetic anhydride until the latter was activated by formation of the complex with a tertiary amine. Similar agglomeration of the zinc occurs in the reductive acetylation of quinones in the absence of an amine. The zinc salt was not noted in previous work[1] because it is destroyed by proton acids. Doubtless other active metals or even the homogeneous mixtures which were previously shown to reduce the adducts would serve as well as zinc; the mechanism of the reduction phase has been discussed.[1]

In connection with this work, the synthesis of 5,8-dihydro-1,4-diacetoxynaphthalenes (IV) from simple diene-quinone adducts has been improved.

(1) R. Gaertner, *J. Am. Chem. Soc.*, **76**, 6150 (1954); also, U. S. Patents 2,750,427, June 12, 1956, and 2,773,883, December 11, 1956.

(2) R. J. W. Byrde and D. Woodcock, *Ann. Appl. Biol.*, **40**, 675 (1953).

(3) L. F. Fieser, W. F. Campbell, E. M. Fry, and M. D. Gates, Jr., *J. Am. Chem. Soc.*, **61**, 3216 (1939).



IV

This reaction had been carried out by simply heating the preformed adduct in acetic anhydride[4a] or by isomerizing and acetylating.[4b–d] It has now been found that both acetic anhydride and isopropenyl acetate are solvents as suitable for the adduction as the recommended acetic acid[5] and that pyridine conveniently catalyzed a rapid exothermic isomerization-acetylation[6] in acetic anhydride without the necessity of isolating the adduct. In the case of the cyclopentadiene-quinone adduct a diacetate with reasonable properties was isolated but the analysis indicated that it had not been freed of the anthrahydroquinone diacetate. The reaction mixture from isoprene and quinone in isopropenyl acetate, when treated with catalytic amounts of sulfuric acid, gave acetone and a 72.5% yield of dihydro diacetate. However, this method was limited in scope, toluquinone and butadiene or 2-methylpentadiene giving only 22–38% yields. Pyridine did not catalyze this reaction.

The synthesis of 1,4-diacetoxynaphthalenes *via* dihydro diacetates using the acetic anhydride-pyridine method, followed by oxidation with sulfur is more convenient and usually gives better yields than either the direct oxidation[5] of the adduct to the quinone followed by reductive acetylation or other less direct methods.[5]

Some reactions typical of double bonds were carried out with the chloranil-butadiene adduct (I). Addition of chlorine and bromine and epoxidation with performic acid occurred in the normal fashion at the 6,7 unsaturation.

EXPERIMENTAL[7]

Reductive acetylation of chloranil and 2,5-dichloroquinone adducts. The reaction mixture usually consisted of 0.02–0.1 mole of preformed adduct[1] with 50% excess zinc dust in fivefold excess acetic anhydride at room temperature. Stoichiometry requires anhydride:zinc:adduct mole ratios of 2:2:1 chloranil adduct and 2:1.5:1 2,5-dichloroquinone adduct. With stirring or swirling about 5 drops of pyridine was added; an exothermic reaction ensued and was controlled by cooling in an ice or water bath. Cooling was especially important with labile adducts such as those from cyclopentadiene and from 2,5-dichloroquinone. If no reaction occurred, the mixture was slowly heated to 50–60° with further dropwise addition of pyridine; if the adduct was impure and contained hydrogen chloride or quinone, additional pyridine was required. When the reaction subsided, addition of more zinc dust or pyridine had no effect and, after brief heating, the reaction was complete. Filtration to remove zinc and cautious addition of water to the warm filtrate to turbidity hydrolyzed the excess anhydride; the products crystallized from the cooled aqueous acetic acid in nearly pure form. They were not noticeably affected by light and air as the dihydro hydroquinones had been. They were recrystallized from methanol-chloroform (decolorized) and sublimed at 1 mm., in some cases, for analysis. The results are summarized in Table I.

Although the chloranil-cyclopentadiene adduct reacted exothermically at 30° in the presence of pyridine, this adduct, when heated slowly with the usual mixture of zinc and acetic anhydride, did not appear to react until, at about 100°, the solution darkened and deposited a black floc. After more of the anhydride had been added and the mixture heated to reflux for 30 min. and cooled to 60°, addition of pyridine caused no reaction. A black infusible powder was the only product.

When tri-*n*-hexylamine and dimethylaniline were added dropwise to the usual reaction mixtures of the chloranil-2,3-dimethylbutadiene adduct, exothermic reactions (rising to 110–120°) gave quantitative and 85% yields, respectively, of the dihydro diacetate, somewhat less pure than the pyridine-catalyzed product.

The application of the pyridine method to two 2,5-dichloroquinone adducts was entirely similar and the results are also listed in Table I.

TABLE I

1,4-DIACETOXY-2,3-DICHLORO-5,8-DIHYDRONAPHTHALENES

			Analyses			
			Calcd.		Found	
Substituent	Yield	M.P., °C.	C	H	C	H
	100	197–199	53.35	3.84	53.42	4.05
5,8-Methano	98	131–132	55.06	3.70	55.29	3.69
6-Methyl	95	166–167.5	54.73	4.29	54.92	4.37
5,7-Dimethyl	74	136–137.5	55.99	4.70	56.49	5.00
6,7-Dimethyl	98	239–241	55.99	4.70	56.27	5.11
2-CHLORO DERIVATIVES						
	88	138–139	59.90	4.67	60.17	4.87
					60.29	4.91
6,7-Dimethyl	84	159–160	62.24	5.55	62.88	5.83

Reactions of the dihydro diacetates. Oxidation of the dihydro compounds to aromatic products was carried out by two procedures:

(*a*) A warm solution of 2,3-dichloro-5,8-dihydro-1,4-diacetoxynaphthalene (1.0 g.) in 10 ml. of acetic acid was treated dropwise with a solution of 1.0 g. of chromic acid in the minimum water with cooling to maintain 90–100°. Addition of water, filtration, and recrystallization from chloroform-alcohol gave 0.50 g. of 1,4-diacetoxy-2,3-dichloronaphthalene, identical with the product[8] (m.p. 236–238°) obtained by reductive acetylation (55% yield) of 2,3-dichloro-1,4-naphthoquinone.

(*b*) Dehydrogenation of 2-chloro-1,4-diacetoxy-5,8-dihydro-6,7-dimethylnaphthalene (3.1 g.) with 0.32 g. of roll sulfur at 230–240° for 50 min. gave, from methanol, 1.43 g

(4a) O. Diels and K. Alder, *Ber.*, **62B**, 2337 (1929). Easily reversed adductions, *e.g.*, "monocyclopentadiene-quinone," gave mediocre yields of bismethyleneoctahydroanthrahydroquinone diacetate by reversal, bis adduction, isomerization-acetylation, and oxidation; yields of diacetates from stable adducts were seldom specified but were probably good. (b) C.-K. Chuang and C.-T. Han, *Ber.*, **68B**, 876 (1935). (c) M. L. Tamayo and J. L. Leon, *J. Chem. Soc.*, 1499 (1948). (d) H. v. Euler and H. Hasselquist, *Arkiv Kemi.*, **2**, 367 (1950).

(5) L. F. Fieser, *J. Am. Chem. Soc.*, **70**, 3165 (1948).

(6) This recalls the similar conversion of ketones to enol acetates by, among others, G. O. Smith, *J. Am. Chem. Soc.*, **75**, 1134 (1953).

(7) Melting points are corrected; boiling points are not. Statements of identity indicate lack of depression of mixture melting points unless other data are given.

(8) C. Graebe, *Ann.*, **149**, 14 (1869).

(47%) of 2-chloro-1,4-diacetoxy-6,7-dimethylnaphthalene; a purified sample was colorless; m.p. 141.5–142.5°.

Anal. Calcd. for $C_{16}H_{15}ClO_4$: C, 62.65; H, 4.93. Found: C, 62.79; H, 5.10.

A similar experiment with the 2,3-dichloro-6-methyl compound gave no isolable product.

Hydrogenation of these dihydro compound to tetrahydro derivatives was carried out in acetic acid in a shaker-type apparatus at 3–4 atmospheres and room temperature over Adams' platinum oxide catalyst. The products were isolated by addition of water and recrystallization from methanol: 1,4-diacetoxy-2,3-dichloro-5,6,7,8-tetrahydronaphthalene. m.p. 181–182° (*Anal.* Calcd. for $C_{14}H_{14}Cl_2O_4$: C, 53.01; H, 4.45. Found: C, 52.64; H, 4.51); the 2,3-dichloro-5,8-methylene analog, m.p. 139–140° (*Anal.* Calcd. for $C_{15}H_{14}O_4Cl_2$: C, 54.73; H, 4.29. Found: C, 54.84; H, 4.48); the 2-chloro compound, m.p. 115.5–116.5° (*Anal.* Calcd. for $C_{14}H_{15}ClO_4$: C, 59.47; H, 5.35. Found: C, 59.93; H, 5.67).

Isomerization-acetylation of diene-quinone adducts. 1. Acetic anhydride-pyridine. The preformed adduct could be used but usually it was prepared in acetic anhydride with 0.4 mole for 0.10 mole of the quinone and 0.11 mole of the diene. After standing 2–4 days in the dark at room temperature, the reaction mixture was treated with 1–4 ml. of pyridine dropwise during heating to 40–70°; an exothermic reaction occurred, the temperature rising to 110–130°. Sensitive adducts were best kept below 100° or lower by external cooling. Brief warming was followed by cautious addition of water to hydrolyze the excess anhydride and the rather pure diacetate was allowed to crystallize. Recrystallization from methanol and/or sublimation *in vacuo* was used for analytical samples. The results are tabulated below.

TABLE II

1,4-DIACETOXY-5,8-DIHYDRONAPHTHALENES

Substituents	Yield	M.P., °C.	Analyses Calcd. C	Calcd. H	Found C	Found H
None[3,4a]	99	130.5–131.5	68.28	5.73	68.29	5.95
6-Chloro	98	107–109	59.90	4.67	60.19	4.96
2-Methyl[4b]	91	104–105.5	69.21	6.20	69.57	6.11
6-Methyl	100	104.5–106	69.21	6.20	68.80	6.10
5,8-Methano[a]	62	86–88	66.94	5.56	69.75	5.46
5,7-Dimethyl[4d,a]	57	56–59	70.05	6.61	73.14	6.42
6,7-Dimethyl[4c]	100	126–128	70.05	6.61	70.49	6.47
2,6,7-Trimethyl	97	138–139	70.81	6.99	70.36	6.63
2,6- and 2,7-Dimethyl	88	100–120				
6-Chloro-2-methyl and 7-chloro-2-methyl	83	92–100				

[a] These products doubtless contain diacetates from bisdiene adducts[3] from which they could not be freed completely by usual methods.

2. Isopropenyl acetate.[9] The adducts were prepared similarly (four days) in isopropenyl acetate, 0.75 mole for a 0.25 mole run. The most favorable case examined—that of isoprene with quinone—was studied briefly. Addition of catalytic amounts of toluenesulfonic acid and hydrochloric acid to the mixture had no effect, nor did pyridine catalyze the acetylation. Addition of a total of 2 ml. of concentrated sulfuric acid gave, on careful fractionation, 38.5 g. of acetone. Aspiration of the excess reagent gave a brown residue which solidified; it was dissolved in ether, washed with water, dried, the ether removed, and the solid recrystallized from methanol. The yield of diacetate was 72.5%, m.p. 100–102°. Similarly from isoprene and toluquinone, a 22% yield of a mixture of the 2,6- and 2,7-dimethyldihydro diacetates was isolated; m.p. 102–104°. From butadiene and toluquinone 38% of the diacetate was isolated; m.p. 99–102°. As seen from the melting points, these products were not as pure as those obtained similarly from acetic anhydride; furthermore, they contained colored impurities which were troublesome to remove. With butadiene, quinone gave only a little of the dihydronaphthohydroquinone while 2-methylpentadiene gave a dark oil. Chloroprene gave the adduct with quinone, which was recovered in part after acetylation, and with toluquinone, no identifiable product.

The 6,7-dimethyl diacetate (8.22 g.) was hydrogenated as usual giving 7.95 g. (96%) of 1,4-diacetoxy-6,7-dimethyl-5,6,7,8-tetrahydronaphthalene; m.p. 78.5–80°.

Anal. Calcd. for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30. Found: C, 69.95; H, 6.98.

Aromatization was best accomplished by heating with equimolar amounts of sulfur[5]; thus, at 230–240°, a 92% yield of 1,4-diacetoxy-6-methylnaphthalene, m.p. 98–100°, was obtained. Heating at 325° with palladium-on-charcoal and oxidation with chromic acid in acetic acid at 50° were unsatisfactory.

By reductive acetylation,[3] quinones were converted to the diacetates; 1,4-diacetoxy-5,7-dimethylnaphthalene (66% yield); m.p. 105–108° (*Anal.* Calcd. for $C_{16}H_{16}O_4$: C, 70.60; H, 5.93. Found: C, 70.68; H, 6.02); 1,4-diacetoxy-6-methylnaphthalene (77% yield); m.p. 102–103.5° (*Anal.* Calcd. for $C_{15}H_{14}O_4$: C, 69.76; H, 5.46. Found: C, 70.13; H, 5.67).

Addition reactions of the butadiene-chloranil adduct. Chlorine was passed into the solution of 6 g. of the adduct in 50 ml. of carbon tetrachloride containing a crystal of iodine. The temperature rose to 45° and slowly dropped to 30°. Aspiration of the solvent left an oil which with methanol crystallized after standing for a week. The dichloride (4.4 g.; 59%) formed cream-colored prisms from methanol-chloroform; m.p. 137–138.5°.

Anal. Calcd. for $C_{10}H_6Cl_6O_2$: C, 32.38; H, 1.63. Found: C, 32.66; H, 2.18.

A mixture of the adduct (4.8 g.), a crystal of iodine, 10 ml. of carbon tetrachloride, and 2.6 g. of bromine was aspirated after two days and the residue crystallized from methanol. The dibromide (0.8 g.) formed colorless flat needles; m.p. 174–176°.

Anal. Calcd. for $C_{12}H_6Cl_4Br_2O_2$: C, 26.12; H, 1.32. Found: C, 26.32; H, 1.72.

When a mixture of 6 g. of the adduct and 3 g. of 29% hydrogen peroxide in 50 ml. of 87% formic acid did not appear to react overnight, it was heated to 55–60° during 1 hr. with stirring, an additional 3-ml. portion of the peroxide added, and the solution heated to 75° briefly. Dilution with water precipitated a gummy solid (4.55 g.; 63%); m.p. 90–113°. Repeated recrystallization with loss from chloroform-methanol gave colorless diamonds; m.p. 167.5–169.5°.

Anal. Calcd. for $C_{11}H_8Cl_4O_6$: C, 38.01; H, 1.91. Found: C, 38.55; H, 2.23.

Perbenzoic acid on the adduct gave an intractable mixture which could not be purified. *N*-Bromosuccinimide and perchloromethyl mercaptan with the adduct failed to give crystalline products.

DAYTON, OHIO

(9) H. J. Hagemeyer, Jr., and D. C. Hull, *Ind. Eng. Chem.*, **41**, 2920 (1949), described enol acetate interchange reactions with this reagent.

[COMMUNICATION NO. 1910 FROM THE KODAK RESEARCH LABORATORIES]

Disproportionation of Unsymmetrical Carbonates

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Mixed ethyl and aryl or aralkyl carbonates disproportionate when heated with suitable catalysts, particularly metal alkoxides. Usually, diethyl carbonate is formed, and often the other symmetrical carbonate can be isolated. However, loss of carbon dioxide and other side reactions can take place. The course of the reactions depends on the structure of the carbonates and on the catalyst.

Side reactions of the symmetrical carbonates include polymerization, loss of carbon dioxide, and formation of olefins, alcohols, and ethers. Of the carbonates, the benzyl structure is the one most prone to side reactions. While the β-phenylethyl unit is somewhat more stable, it will degrade to styrene during long reaction times. Phenyl carbonates are also unstable. Cinnamyl and furfuryl derivatives are exceptionally unstable, and readily yield polymers. Tetrahydrofurfuryl carbonates are stable to polymerization, and the symmetrical carbonate is obtained in this case. The allyl system does not disproportionate at its boiling point. It was expected that the 3-phenylpropyl unit would possess enhanced stability, but it was cleaved to the alcohol. The β-phenoxyethyl unit is the most stable carbonate studied with regard to degradation, both during and after the formation of the symmetrical carbonate.

The more alkaline catalysts, such as sodium methoxide and lithium aluminum ethoxide, promote more side reactions than does titanium butoxide, the catalyst of choice.

Symmetrical carbonates have been most often prepared by reaction of an alkoxide with phosgene. We decided to study their formation by ester interchange (Reaction 1).

$$2ROCOR' \underset{}{\overset{\text{cat.}}{\rightleftharpoons}} ROCOR + R'OCOR' \qquad (1)$$

In general, our hope to develop a workable synthesis of symmetrical carbonates was realized. It is more convenient to discuss the detailed behavior of the compounds separately.

Ethyl benzyl carbonate, when treated with lithium aluminum ethoxide, produced diethyl carbonate, dibenzyl ether, and carbon dioxide. No symmetrical carbonate was isolated. Using lithium methoxide catalyst, a small amount of the symmetrical dibenzyl carbonate was obtained. The major product was dibenzyl ether. Sodium methoxide, titanium tetrachloride, titanium butoxide, sodium hydrogen titanium butoxide, strontium methoxide, magnesium methoxide, aluminum isopropoxide, tetraethyl tin, lead borate, and sodium phenoxide produced dibenzyl carbonate, diethyl carbonate, and no dibenzyl ether.

Dibenzyl carbonate, treated with lithium methoxide, produced dibenzyl ether, benzyl alcohol, and water. Lithium aluminum ethoxide produced only dibenzyl ether. On the other hand, magnesium methoxide, during much longer reaction times, produced benzaldehyde, toluene, dibenzyl ether, water, and carbon dioxide. Shorter reaction times, comparable to those used for the first two catalysts, yielded only dibenzyl carbonate. Apparently, degradation reactions of dibenzyl ether were much slower in the presence of magnesium methoxide than with either lithium aluminum ethylate or lithium methoxide. When dibenzyl ether itself was treated with lithium methoxide under the same reaction conditions, a small amount of benzaldehyde and toluene was noted. The identity and appearance of degradation products of benzyl alcohol, which were particularly noticeable during the longer heating times and with the more alkaline catalysts, are related to the work of Lachman,[1] who studied the decomposition of dibenzyl ether and benzyl alcohol at elevated temperatures.

$$(C_6H_5CH_2)_2O \xrightarrow[210°]{\text{5 days}} C_6H_5CH_3 + C_6H_5CHO \text{ (no water)}$$

$$C_6H_5CH_2OH \xrightarrow[\text{1 hour}]{\text{190° NaOH}} C_6H_5CO_2Na + (C_6H_5CH_2)_2O$$

$$C_6H_5CH_2OH \xrightarrow[\text{Sealed tube}]{210°} C_6H_5CO_2H + (C_6H_5CH_2)_2O + C_6H_5CH_3$$

Related studies by Cannizzaro[2] and Lowe[3] illustrated the disproportionation of benzyl alcohol.

$$C_6H_5CH_2OH \xrightarrow[\text{anhydride}]{\text{Boric}} C_6H_5CH_2OCH_2C_6H_5$$

$$C_6H_5CH_2OH \xrightarrow[\substack{H_2O\\ \text{reflux}}]{\text{NaOH}} C_6H_5CH_2OCH_2C_6H_5$$

Ethyl β-phenylethyl carbonate, smoothly disproportionated in the presence of titanium butoxide yielded 82% of the desired product. Lithium aluminum butoxide yielded 74%, along with some carbon dioxide and styrene.

$$C_6H_5CH_2CH_2OCO_2C_2H_5 \xrightarrow{Ti(OC_4H_9)_4} (C_6H_5CH_2CH_2)_2CO$$

$$C_6H_5CH_2CH_2OCO_2C_2H_5 \xrightarrow{LiAl(OC_4H_9)_4} (C_6H_5CH_2CH_2O)_2CO + C_6H_5CH{=}CH_2$$

Previous work[4] indicated that only small amounts of styrene were produced by the noncatalyzed pyro-

(1) A. Lachman, *J. Am. Chem. Soc.*, 45, 2356 (1923).
(2) S. Cannizzaro, *Ann.*, 92, 113 (1854).
(3) C. W. Lowe, *Ann.*, 241, 374 (1887).
(4) J. L. R. Williams, K. R. Dunham, and T. M. Laakso, *J. Org. Chem.*, 23, 676 (1958).

lytic decomposition of ethyl β-phenylethyl carbonate at 250°.

Di(β-phenylethyl) carbonate, heated to 250°, with no catalyst, yielded 1.4% of styrene and 78% recovered carbonate. Lithium aluminum ethoxide produced 50% styrene, some polystyrene, and 2% of the starting material. Titanium butoxide gave no styrene, and 84% of the carbonate was recovered.

γ-Phenylpropyl ethyl carbonate, heated with lithium aluminum ethoxide, yielded 59% of γ-phenylpropyl alcohol, and no high-boiling fraction was detected. This result is in accord with the work of Ritchie,[5] who described experiments dealing with the pyrolysis of carbonic esters, in which alkyl carbonates produced an alcohol, an olefin, and carbon dioxide. Unsymmetrical carbonates gave mixtures of all possible alcohols and olefins.

Bis(γ-phenylpropyl) carbonate suffered little degradation in the presence of sodium hydrogen titanium butoxide or titanium butoxide, having been recovered in 84 and 83% yield.

Allyl ethyl carbonate, refluxed with lithium aluminum ethoxide, was unchanged; 94% of the starting material was recovered.

Cinnamyl ethyl carbonate, treated either with lithium aluminum ethoxide or strontium methoxide, lost carbon dioxide. The rate of release of carbon dioxide, however, was much more rapid in the case of lithium aluminum ethoxide. Unfortunately, further decomposition and polymerization occurred during distillation, and no identification of the products was possible.

Ethyl phenyl carbonate, treated with lithium aluminum ethoxide or strontium methoxide, produced low yields of symmetrical carbonate. The odor of phenol was noted in both cases. Phenetole was isolated in 30% yield from the first run, and may have been present in the second. Formation of phenetole is analogous to the conversion of β-napthyl ethyl carbonate by heating, to β-ethoxynaphthalene.[6]

Ethyl furfuryl carbonate, treated with titanium butoxide, strontium methoxide, or lithium aluminum ethoxide, yielded polymers. Small amounts of a mixture of diethyl carbonate, ethanol, and furfuryl alcohol were obtained.

Ethyl tetrahydrofurfuryl carbonate, with either strontium methoxide or lithium aluminum ethoxide, gave 69.8 and 62.8% yields of the symmetrical carbonate, with no evidence of release of carbon dioxide.

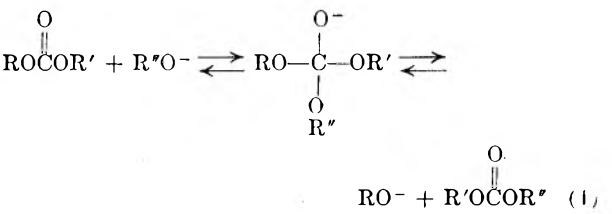
Ethyl β-phenoxyethyl carbonate yielded 76 to 92% of the symmetrical carbonate with the four catalysts studied: strontium methoxide, titanium butoxide, lithium aluminum ethoxide, and sodium hydrogen titanium butoxide. No carbon dioxide was formed, and the material balance was the best in the study.

(5) P. D. Ritchie, *J. Chem. Soc.*, 1054 (1935).

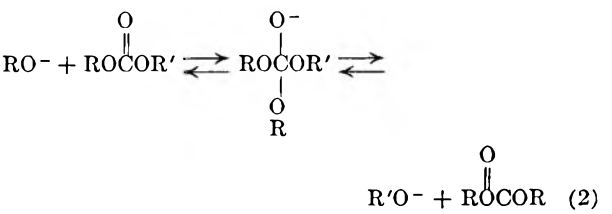
(6) K. C. Tsou and A. M. Seligmann, *J. Am. Chem. Soc.*, **76**, 3704 (1954).

It is thus obvious that structure and catalyst exert important influences on the course of the interchange reaction.

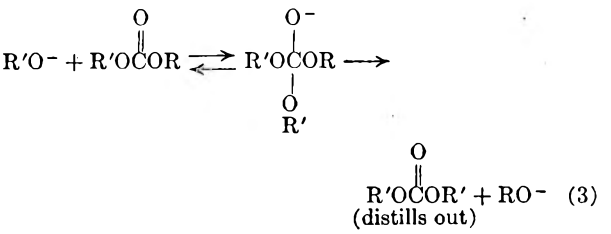
A general mechanism for base-catalyzed interchange is suggested in Equations 1 to 3. The catalyst ion is $R''O^-$.



Equation 1 describes the equilibrium of the catalyst with the first of the radicals of the unsymmetrical carbonate; Equation 2 that with the second, and equation 3 shows a third equilibrium.



If one symmetrical carbonate is removed as it forms, the equilibrium will be shifted towards formation of the two symmetrical carbonates, and the residue will be the pure, high-boiling symmetrical carbonate.



With a Lewis acid (for instance, titanium alkoxide) the reaction path could proceed similarly (Equations 4 and 5).

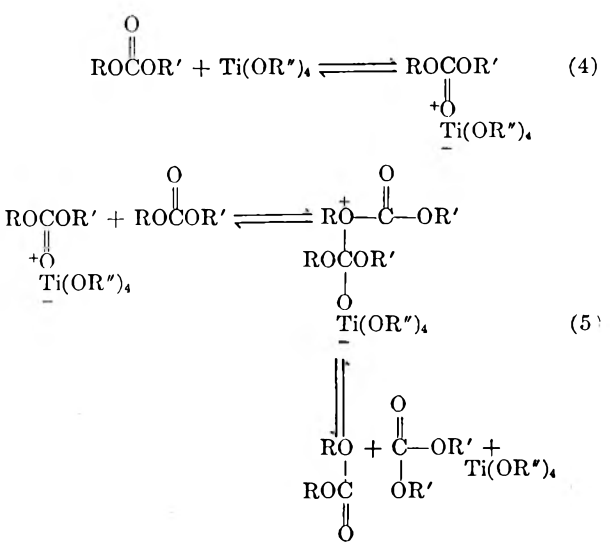


TABLE I. REACTIONS OF CARBONATES

Class	Compound	Run	Catalyst	Amount	Time (Min.)	Products
A	$C_6H_5CH_2OCO_2C_2H_5$[g]					$(C_6H_5CH_2)_2O$
	100 g. (0.55 mole)	1	$LiAl(OC_2H_5)_4$[a]	1.0 ml.	1.95	79
		2	$LiOCH_3$[b]	10.0 ml.	120	57.5
		3	$NaOCH_3$[f]	0.1 g.	155	–
		4	$TiCl_4$	0.5 ml.	105	–
		5	$Ti(OC_4H_9)_4$	0.1 ml.	100	–
		6	$NaHTi(OC_4H_9)_6$[c]	10.0 ml.	180	–
		7	$Sr(OCH_3)_2$[d]	10.0 ml.	90	–
		8	$Mg(OCH_3)_2$[e]	10.0 ml.	22	–
		9	$Al(OC_3H_7)_3$[f]	0.1 g.	75	–
		10	$(C_2H_5)_4Sn$	3.0 ml.	360	–
		11	Lead borate[c]	0.1 g.	50	–
		12	$NaOC_6H_5$	1.0 g.	90	–
	$(C_6H_5CH_2O)_2CO$[h]					
	50 g. (0.21 mole)	13	$LiOCH_3$[b]	10.0 ml.	165	28.8
		14	$LiAl(OC_2H_5)_4$[a]	4.0 ml.	130	99
		15	$Mg(OCH_3)_2$[a]	10.0 ml.	1080	58.5
	$(C_6H_5CH_2)_2O$[i]					C_6H_5CHO
	40 g. (0.2 mole)	16	$LiOCH_3$[b]	10.0 ml.	195	Trace
B	$C_6H_5CH_2CH_2OCO_2C_2H_5$[j]					$(C_6H_5CH_2CH_2O)_2CO$
	100 g. (0.52 mole)	17	$LiAl(OC_2H_5)_4$[a]		120	61
		18	$Ti(OC_4H_9)_4$	0.3 ml.	120	64
	$(C_6H_5CH_2CH_2O)_2CO$					$(C_6H_5CH_2CH_2O)_2CO$
	50 g. (0.26 mole)	19	Nil		420	78
		20	$LiAl(OC_2H_5)_4$[a]	10.0 ml.	420	2
		21	$Ti(OC_4H_9)_4$	0.3 ml.	180	84
C	$C_6H_5CH_2CH_2CH_2OCO_2C_2H_5$					$(C_6H_5CH_2CH_2CH_2O)_2CO$
	100 g. (0.48 mole)	22	$LiAl(OC_2H_5)_4$[a]	10.0 ml.	60	–
		23	$Ti(OC_4H_9)_4$	0.1 ml.	60	84.5
		24	$NaHTi(OC_4H_9)_6$	10.0 ml.	50	83
D	$CH_2{=}CHCH_2OCO_2C_2H_5$[k]					$CH_2{=}CHCH_2OCO_2C_2H_5$
	100 g. (0.77 mole)	25	$LiAl(OC_2H_5)_4$[a]	10.0 ml.	70	94 (recovery
E	$C_6H_5CH{=}CH{-}CH_2OCO_2C_2H_5$[l]					
	100 g. (0.48 mole)	26	$Sr(OCH_3)_2$[d]	10.0 ml.	175)	No clear fractions, polymer-
		27	$LiAl(OC_2H_5)_4$[a]	10.0 ml.	40)	with loss of CO_2
F	$C_6H_5OCO_2C_2H_5$[i]					C_6H_5OH
	100 g. (0.62 mole)	28	$LiAl(OC_2H_5)_4$[a]	10.0 ml.	180	Trace
		29	$Sr(OCH_3)_2$[d]	10.0 ml.	200	Trace
G	$C_4H_3OCO_2C_2H_5$[o]					$C_4H_3OCH_2OH$
	100 g. (0.54 mole)	30	$Sr(OCH_3)_2$[d]	10.0 ml.	85)	+
					)	Polymer on distillation
		31	$LiAl(OC_2H_5)_4$[a]	10.0 ml.	70)	+
		32	$Ti(OC_4H_9)_4$	0.3 ml.		
H	$C_4H_7OCH_2OCO_2C_2H_5$[m]					$(C_4H_7OCH_2O)_2CO$[m]
	100 g. (0.56 mole)	33	$Sr(OCH_3)_2$[d]	10.0 ml.	15	69.8
		34	$LiAl(OC_2H_5)_4$[a]	10.0 ml.	75	62.8
I	$C_6H_5OCH_2CH_2OCO_2C_2H_5$[n]					$(C_6H_5OCH_2CH_2O)_2CO$[n]
	100 g. (0.48 mole)	35	$Sr(OCH_3)_2$[d]	10.0 ml.	65	60.8
		36	$Ti(OC_4H_9)_4$	0.6 ml.	45	62.7
		37	$LiAl(OC_2H_5)_4$[a]	10.0 ml.	75	65.5
		38	$NaHTi(OC_4H_9)_6$[c]	10.0 ml.	90	73.0

Equations 1 to 5 fail to explain the side reactions of many of the carbonates. These may arise as a consequence of subsequent reactions of carbanions formed as shown in Equations 6 to 8.

$$ArCH_2CH_2O\overset{O}{\overset{\|}{C}}OR' + Ti(OR'')_4 \rightleftharpoons ArCHCH_2O\overset{O}{\overset{\|}{C}}OR' + [HTi(OR'')_4]^+ \quad (6)$$

$$ArCHCH_2O\overset{O}{\overset{\|}{C}}{-}OR' \longrightarrow ArCH{=}CH_2 + CO_2 + R'O^- \quad (7)$$

$$R'O^- + [HTi(OR'')_4]^+ \longrightarrow R'OH + Ti(OR'')_4 \quad (8)$$

EXPERIMENTAL

Decomposition studies. Samples of various carbonates were heated in glass equipment consisting of flask, Vigreux column, and partial take-off head. Silicone oil baths were used, and held throughout the decomposition period at 250°. Heating mantles were used to distill the products from the reaction flask. The results are summarized in Table I.

Preparation of carbonate intermediates. Compounds not previously reported in the literature were prepared as in the following example:

Ethyl tetrahydrofurfuryl carbonate. To a stirred mixture of 500 g. (5.0 moles) of tetrahydrofurfuryl alcohol in 500 g. of pyridine, was added 600 g. (5.5 moles) of ethyl chlorocarbonate at 10–20°. After the addition was complete, the mixture was stirred for 1 hr. One liter of benzene was added,

TABLE I. REACTIONS OF CARBONATES (*Continued*)

Conversion (%) and Recoveries						
$(C_6H_5CH_2O)_2CO$	$(C_2H_5O)_2CO$	CO_2				
–	+	+				
Trace	+	+				
70.5	+	–				
89	+	–				
90	+	–				
88	+	–				
81.8	+	–				
79.5	+	–				
49	+	–				
72	+	–				
75	+	–				
75	+	–				
			$C_6H_5CH_2OH$	C_6H_5CHO	$C_6H_5CH_3$	H_2O
41		+	–	–	–	–
–		+	–	–	–	–
–		+	–	18	23.8	0.5
$C_6H_5CH_3$						
Trace						
$C_2H_5CH_2CH_2OCO_2C_2H_5$		$C_6H_5CH{=}CH_2$		$(C_2H_5O)_2CO$	CO_2	
18		Trace		+	Trace	
22	–	–		+	–	
$C_6H_5CH{=}CH_2$	$(C_2H_5O)_2CO$	CO_2				
1.4	+	+				
>50	+	+				
–	+	+				
$C_6H_5CH_2CH_2CH_2OH$						
59	+	–				
		–				
		–				
after heating at its boiling point)						
ised during distillation						
$C_6H_5OC_2H_5$	$(C_6H_5O)_2CO$					
–	36.8					
30	28					
$(C_2H_5O)_2CO$	CO_2	C_2H_5OH				
–	+	+				
–	+	+				
+	+	+				
$(C_2H_5O)_2CO$	CO_2					
+	+					
+	+					
$C_6H_5{}^nOCH_2CH_2OCO_2C_2H_5$						
20						
32						
20						
15						

[a] Lithium aluminum hydride, 1.0 g. in 100 ml. of absolute ethanol. [b] Lithium methoxide, 1.0 g. in 100 ml. of absolute ethanol. [c] Solution of 0.5 g. of sodium and 7.8 g. of titanium butoxide in 200 ml. of *n*-butyl alcohol. [d] Solution of 1.0 g. of strontium in 100 ml. of methanol. [e] Solution of 1.0 g. of magnesium in 100 ml. of methanol. [f] Catalyst was not completely soluble. [g] P. Schving and S. Sabetay, *Bull. Soc. Chim.*, **43**, 857 (1928). [h] C. A. Bischoff, *Ber.*, **36**, 159 (1903). [i] G. M. Bennett and G. H. Willis, *J. Chem. Soc.*, 2305 (1928). [j] P. Schving and S. Sabetay, *Bull. Soc. Chim.*, **43**, 1341 (1928). [k] D. E. Adelson and H. Dannenberg, U. S. Pat. **2,595,214** (1952). [l] L. Claisen, *Ber.*,**27**, 3182 (1894). [m] Tetrahydrofurfuryl. [n] Phenyl. [o] Furyl.

TABLE II. UNSYMMETRICAL CARBONATES $C_2H_5OCO_2R$

R	Yield, %	B.P.	M.P.	n_D^{25}	Analysis Calcd. C	Calcd. H	Found C	Found H
$C_6H_5OCH_2CH_2$—	86		45°		62.9	6.7	63.3	6.7
$C_6H_5(CH_2)_3$—	83	130° (2 mm.)		1.4860	69.2	7.8	69.7	8.2
$C_4H_3OCH_2$—[a]	77	66° (0.6 mm.)		1.4370	56.5	5.6	55.6	5.8
$C_4H_7OCH_2$—[b]	76	70° (1 mm.)		1.4560	55.2	8.0	54.8	8.4

[a] Furfuryl. [b] Tetrahydrofurfuryl.

TABLE III

SYMMETRICAL CARBONATES $ROCO_2R$

R	B.P.	M.P.	n_D^{25}	Analysis Calcd. C	Calcd. H	Found C	Found H
$C_6H_5OCH_2CH_2$—	180–183° (0.4 mm.)	92–93°		67.6	6.0	67.5	5.8
$C_6H_5(CH_2)_3$—	176° (0.4 mm.)		1.5318	76.5	7.4	76.9	6.9
$C_4H_7OCH_2$—[a]	114°		1.4658	55.5	7.5	55.9	7.7

[a] Tetrahydrofurfuryl.

and the mixture was washed successively with water, dilute hydrochloric acid, water, dilute sodium carbonate, and water. The organic material was dried over calcium chloride and distilled to give 658 g. (76.0% of theoretical) of ethyl tetrahydrofurfuryl carbonate. The physical properties are listed in Table II.

Table III summarizes the properties of new symmetrical carbonates isolated from the disproportionation reactions of the unsymmetrical carbonates.

Catalysts. The catalysts were prepared or purified in a nitrogen atmosphere under dry conditions.

ROCHESTER, N. Y.

[CONTRIBUTION FROM THE RESEARCH LABORATORY, MCLAUGHLIN GORMLEY KING CO.]

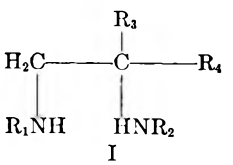
5-Membered Heterocyclic Compounds Derived from Piperonal. I. A Study of the Reactions between Piperonal and 1,2-Diamines

PETER F. EPSTEIN

Received August 19, 1958

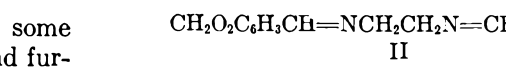
A number of 1,2-diamines were allowed to react with piperonal. The nature of the products obtained varied with the type of amine used. When both the amine groups were primary, a di-Schiff's base was formed; with one primary and one secondary amine group the product was an imidazolidine; while in the case of a di-secondary amine there was either no reaction or an imidazolidine was formed, depending on the nature of the substituent groups.

Riebsomer[1] described the formation of some imidazolidines derived from benzaldehyde and furfural. Other workers[2–6] have reported similar results. It seemed to the author to be of interest to discover if the less reactive piperonal would behave in a similar manner, and accordingly attempts were made to condense piperonal with a number of 1,2-diamines of the general Formula I.



I

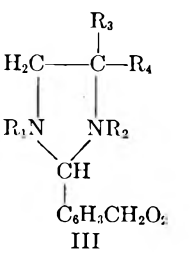
In the simplest case of all, using 1,2-diaminoethane (I; $R_1 = R_2 = R_3 = R_4 = H$) the only product which could be isolated was the di-Schiff's base *N,N'*-di(3,4-methylenedioxybenzal)-1,2-diaminoethane (II).



II

This result was obtained regardless of the proportions of reagents used, and in no case could any of the imidazolidine be isolated. These findings agree with the work of van Alphen[5] regarding the corresponding benzaldehyde compounds.

In the case of diamines with one primary and one secondary group, of the type used by Riebsomer[1] the reaction proceeded smoothly to give imidazolidines. Thus, for example, N_1-phenyl-2-(3,4-methylenedioxyphenyl)-4,4-dimethylimidazolidine.



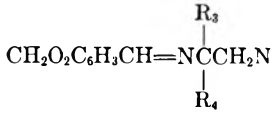
III

(II; R_1 = Ph, R_2 = H, $R_3 = R_4$ = Me) was prepared in 89% yield from piperonal and 1-phenyl-

(1) J. L. Riebsomer, *J. Org. Chem.*, **15**, 237 (1950).
(2) F. Moos, *Ber.*, **20**, 732 (1887).
(3) C. A. Bischoff, *Ber.*, **31**, 3248 (1898).
(4) M. Scholtz and K. Jaross, *Ber.*, **34**, 1504 (1901).
(5) J. van Alphen, *Rec. Trav. Chim.*, **54**, 93 (1935).
(6) W. L. C. Veer, *Rec. Trav. Chim.*, **57**, 989 (1938).

amino-2,2-dimethyl-2-aminoethane (I; R_1 = Ph, R_2 = H, R_3 = R_4 = Me).

The compounds formed in this manner were colorless crystalline solids with well-defined melting points. Their identity as imidazolidines [rather than the corresponding mono Schiff's bases of (IV), having identical empirical formulas], was established



IV

partly by analogy with the results of Riebsomer[1] and partly by their stability to reduction with sodium and ethanol. Lob[7] showed that under these conditions Schiff's bases are reduced to secondary amines while imidazolidines are not affected. In the present investigation the presumed imidazolidines were recovered unchanged after treatment with sodium and ethanol, which is in accordance with the above findings.

It was found impossible to prepare derivatives (*e.g.* benzoyl or acetyl) of these imidazolidines for further investigation. This also agrees with the experiences of Riebsomer.[1]

In the case of diamines with two secondary amine groups (I, R_1 = R_2 = alkyl, cycloalkyl, aryl or aralkyl, R_3 = R_4 = H) the results varied. When R_1 and R_2 are aryl, aralkyl, or cycloalkyl groups (*e.g.* phenyl, benzyl, 3,4-methylenedioxybenzyl, or cyclohexyl) the corresponding imidazolidines were formed as expected. (It is to be noted that in this case there is no possibility of Schiff's base formation.) When R_1 and R_2 were simple alkyl groups, however, no reaction occurred under the conditions used for this series of experiments. In these cases the starting materials were recovered unchanged in all experiments with the exception of one in which *N,N'*-di-*n*-butyl-1,2-diaminoethane (I, R_1 = R_2 = *n*-Bu; R_3 = R_4 = H) was used. This led to a compound whose melting point was much higher than expected for an imidazolidine; and which was shown by element analysis to be definitely not the desired compound. Its nature was not further investigated.

The di-secondary amines used in these experiments were prepared either by hydrogenation of the corresponding di-Schiff's base[7,8] (itself prepared by condensing the appropriate aldehyde with 1,2-diaminoethane) or by treating a suitable primary amine with 1,2-dichloroethane[9] or 1,2-dibromoethane.[10]

EXPERIMENTAL

All melting points are uncorrected. Microanalyses by Clark Microanalytical Laboratory, Urbana, Ill.

(7) G. Lob, *Rec. Trav. Chim.*, **55**, 859 (1936).
(8) A. Mason, *Ber.*, **20**, 270 (1887).
(9) G. H. Bennett, *J. Chem. Soc.*, **576** (1919).
(10) W. R. Boon, *J. Chem. Soc.*, 307 (1947).

A. Amine with two primary amine groups.

N,N'-di(3,4-methylenedioxybenzal)1,2-diaminoethane. A solution of piperonal (30 g.) and 1,2-diaminoethane monohydrate (7.8 g.) in ethanol (50 ml.) was heated under reflux for 1 hr. On cooling, white crystals of the Schiff's base were formed, and were filtered off and dried. Yield 33.2 g. = 95%, m.p. 178–179° (from ethanol).

Anal. Calcd. for $C_{18}H_{16}N_2O_4$: C, 66.67; H, 4.94; N, 8.64. Found: C, 66.57; H, 4.96; N, 8.86.

In similar experiments performed as above but using twice and four times the above quantities of 1,2-diaminoethane monohydrate only the same compound was isolated, and in each case 95% of the piperonal used could be accounted for as the Schiff's base.

B. Amines with one primary and one secondary amine group. One example will suffice to illustrate the method of preparation of the imidazolidines listed in Table I.

N_1-isopropyl-2-(3,4-methylenedioxyphenyl)-4,4-dimethylimidazolidine (III, R_1 = *i*-Pr, R_2 = H, R_3 = R_4 = Me). A mixture of 1-isopropylamino-2,2-dimethyl-2-aminoethane (26 g.), piperonal (30 g.) and benzene (100 ml.) was heated together under reflux. The vapors were passed through a Dean-Stark water separator reflux head inserted between the reaction vessel and the condenser, thus enabling the water formed in the reaction to be collected and measured. The reaction was continued until the theoretical amount of water was evolved (2 hr.) The benzene was removed and the residue distilled, b.p. 157°/6 m.m. The distillate solidified to a waxy solid m.p. 37°–38°, soluble in all the usual organic solvents but insoluble in water. Yield 52.6 g. (quantitative).

Anal. Calcd. for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45; N, 10.68. Found: C, 68.65; H, 8.44; N, 10.51.

In the case of the other compounds listed in Table I, the products solidified as soon as the benzene was removed and distillation was not necessary. They were recrystallized from ethanol.

C. Amines with two secondary amine groups. Those imidazolidines listed in Table I which were prepared from di-secondary amines were made as in the example quoted. In addition, the following di-secondary amines were treated with piperonal under the same conditions as above. In each case only the starting materials were recovered: *N,N'*-diethyl-1,2-diaminoethane, *N,N'*-di*iso*propyl-1,2-diaminoethane, *N,N'*-diallyl-1,2-diaminoethane, *N,N'*-di-*tert*-butyl-1,2-diaminoethane, *N,N'*-di(2-ethyl-butyl)-1,2-diaminoethane.

In the further case of *N,N'*-di-*n*-butyl-1,2-diaminoethane, also treated as in the example quoted, a solid of m. p. 179° (after purification) was formed.

Anal. Calcd. for $C_{18}H_{28}N_2O_2$: C, 71.02; H, 9.27; N, 9.20. Found: C, 66.72; H, 4.90; N, 8.59. This is obviously not the desired imidazolidine. The nature of this compound was not further investigated.

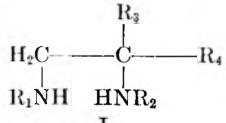
The di-secondary amines required were prepared either by the reduction of the corresponding Schiff's base[7,8] (Method 1) or by the action of the appropriate primary amine on an ethane-1,2-dichloride[9,10] (Method 2). They are listed in Table II.

One example will suffice to illustrate the method of preparation of these disecondary amines by Method 1. *N,N'-dibenzyl-1,2-diaminoethane*[7] (I, R_1 = R_2 = $-CH_2C_6H_5$; R_3 = R_4 = H). A solution of *N,N'*-dibenzal-1,2-diaminoethane[8] (19.3 g.) in methanol (50 ml.) was mixed with a catalyst consisting of a 10% suspension of palladium black on barium sulphate (5 g.) and hydrogenated with shaking at room temperature and an initial hydrogen pressure of 40 p.s.i.. When the reduction was complete (3 hr.) the catalyst was filtered off, the methanol removed, and the residue distilled, b. p. 203°C./2 m.m. Yield 17.1 g. = 87.1%.

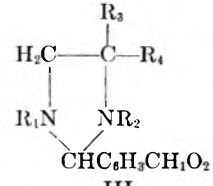
Attempted benzoylation of an imidazolidine. N_1-isopropyl-2-(3,4-methylenedioxyphenyl)-4,4,-dimethyl-imidazolidine (III, R_1 = *i*-Pr, R_2 = H, R_3 = R_4 = Me) was treated with benzoyl chloride under the normal conditions of the Schotten-Baumann reaction. The only product formed was the

TABLE I

IMIDAZOLIDINES



I

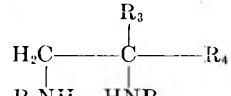


III

A. Amine Used	Radicals in I & III above				Formula of Product	M.P. °C.	Yield, %	Analysis					
								C		H		N	
	R_1	R_2	R_3	R_4				Calcd.	Found	Calcd.	Found	Calcd.	Found
a. Primary-secondary amines													
1-Isopropylamino-2,2-dimethyl-2-aminoethane	Isopropyl	H	Me	Me	$C_{16}H_{22}N_2O_2$	37–38	Quant.	68.67	68.65	8.45	8.44	10.68	10.5
1-Phenylamino-2,2-dimethyl-2-aminoethane	Phenyl	H	Me	Me	$C_{18}H_{20}N_2O_2$	102	89.0	72.95	72.81	6.80	6.86	9.45	9.45
1-(2-Hydroxyethylamino)-2,2-dimethyl-2-aminoethane	$HOCH_2CH_2$	H	Me	Me	$C_{14}H_{20}N_2O_3$	81–82	91.6	63.62	63.36	7.63	7.56		
1-(2-Hydroxypropylamino)-2,2-dimethyl-2-aminoethane	$HOCH(CH_3)CH_2$—	H	Me	Me	$C_{15}H_{22}N_2O_3$	89–90	93.0	64.72	64.55	7.97	7.80	10.06	9.75
1-(1,1-Dimethyl-2-hydroxyethyl-amino)-2,2-dimethyl-2-aminoethane	$HOCH_2CMe_2$	H	Me	Me	$C_{16}H_{24}N_2O_3$	78	77.0	65.73	65.56	8.27	8.25	9.58	9.44
b. Di-secondary amines													
N,N'-diphenyl-1,2-diaminoethane	Phenyl	Ph	H	H	$C_{22}H_{20}N_2O_2$	155	Quant.	76.72	76.85	5.85	5.71	8.13	8.17
N,N'-dicyclohexyl-1,2-diaminoethane	Cyclohexyl	Cyclohexyl	H	H	$C_{22}H_{32}N_2O_2$	120	86.0	74.12	73.97	9.05	8.85	7.86	7.76
N,N'-dibenzyl-1,2-diaminoethane	Benzyl	Benzyl	H	H	$C_{24}H_{24}N_2O_2$	112	Quant.	77.39	77.59	6.49	6.27	7.52	7.32
N,N'-di(3,4-methylene dioxybenzy)-1,2-diaminoethane	3,4-Methylene-dioxybenzyl	3,4-Methylene-dioxy-benzyl	H	H	$C_{28}H_{24}N_2O_6$	155–156	Quant.	67.82	67.91	5.25	5.04	6.08	6.28

TABLE II

DI-SECONDARY AMINES



I

Amine	Method of Preparation	Schiff's M.P., ° C. Base	Dihalide Used	Over-all Yield, %	B. P., ° C.	R in I			
						R_1	R_2	R_3	R_4
N,N'-dibenzyl-1,2-diaminoethane	1	57–58	...	87.1	203/2 m.m.	$-CH_2Ph$	$-CH_2Ph$	H	
N,N'-di-(3,4-methylenedioxybenzyl)-1,2-diaminoethane	1	178–179	...	76.3	45[a]	$-CH_2C_6H_3CH_2O_2$	$-CH_2C_6H_3CH_2O_2$	H	
N,N'-di-*n*-butyl-1,2-diaminoethane	1[b]	184/18 m.m.[c]	...	86.5	265/760 m.m. 167/40 m.m.	*n*-Bu	*n*-Bu	H	H
N,N'-di-ethyl-1,2-diaminoethane	1[d]	Not isolated	...	40.3	60/8 m.m.	Et	Et	H	H
N,N'-di-cycohexyl-1,2-diaminoethane	2	...	1-2-Dibromo-ethane	59.3	89[a]	Cyclohexyl	Cyclohexyl	H	H
N,N'-diphenyl-1,2-diaminoethane	2	...	1-2-Dichloro-ethane	89.9	64–64.5	Ph	Ph	H	
N,N'-di-*iso*propyl-1,2-diaminoethane	2	...	1-2-Dibromo-ethane	62.0	169–173/750 m.m.	*i*-Pr	*i*-Pr	H	H
N,N'-diallyl-1,2-diaminoethane	2	...	1-2-Dibromo-ethane	64.2	198–201/760 m.m.	Allyl	Allyl	H	H
N,N'-di-(2-ethyl-butyl)-1,2-diamino-ethane	2	...	1-2-Dibromo-ethane	38.0	116/5 m.m.	$-CH(Et)C_3H_7$	$-CH(Et)C_3H_7$	H	H
N,N'-di-*tert*-butyl-1,2-diaminoethane	2	...	1-2-Dibromo-ethane	61.0	193/760 m.m.	*tert* Bu	*tert* Bu	H	H

[a] M. p. [b] Using butyraldehyde. [c] B. p. [d] Using acetaldehyde.

dibenzoyl derivative of 1-isopropylamino-2,2-dimethyl-2-aminoethane with m.p. 146°. It gave a mixed m.p. 146° with an authentic sample. (Riebsomer[1] gives m.p. 146°–147°.)

Attempted acetylation of an imidazolidine. N_1-isopropyl-2-(3,4-methylenedioxyphenyl)-4,4-dimethyl-imidazolidine (III, R_1 = *i*-Pr, R_2 = H, R_3 = R_4 = Me) was treated with acetyl chloride under the usual conditions for acetylating an amine. No solid product could be isolated. The mixture, even −10°, formed a sticky tar which decomposed on attempted distillation.

Attempted hydrogenation of an imidazolidine using sodium and ethanol. To a solution of N_1-phenyl-2-(3,4-methylenedioxyphenyl)-4,4-dimethyl-imidazolidine (III, R_1 = Ph, R_2 = H, R_3 = R_4 = Me) (29.6 g.) in very dry ethanol[11] (250 ml.) was added sodium (9.2 g.) in large pieces at such a rate that a vigorous reflux was maintained. When all the sodium had been added and the reaction began to subside, the mixture was heated under gentle reflux till the last traces of sodium dissolved (30 min.). The mixture was cooled and poured on to ice (250 g.) and the alcohol removed under reduced pressure at 40°. On cooling white crystals (27.3 g.) were formed, which after purification melted at 102°. Mixed m.p. with starting material 102°; showing that only the unchanged starting material could be recovered.

(11) H. Lund and J. Bjerrum, *Ber.*, 64B, 210 (1931).

Acknowledgment. The author is pleased to express his appreciation to the Research Laboratory of Commercial Solvents Corporation for the generous gift of samples of some of the 1,2-diamines used in this investigation.

MINNEAPOLIS 14, MINN.

[CONTRIBUTION FROM THE INSTITUTE OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF CHICAGO]

Metal Salt-Induced Homolytic Reactions. I. A New Method of Introducing Peroxy Groups into Organic Molecules[1,2]

M. S. KHARASCH[3] AND ANDREW FONO[4]

Received July 30, 1958

A new and general method for the introduction of alkyl and aralkyl peroxy groups (ROO) into many types of organic molecules has been developed. This is accomplished by the use of a hydroperoxide and a copper, cobalt, or manganese salt catalyst. The versatility of this method is indicated by the fact that compounds of such diverse structure as cyclohexene, octene-1, cumene, α-methylcyclohexanone, cyclohexanone, dimethylaniline, xylene, and dioxane give good to excellent yields of the unsymmetrical peroxides.

Work done at this laboratory indicates that the metal-induced reaction of a hydroperoxide with organic compounds is as effective in introducing ROO groups as *N*-bromosuccinimide is in introducing bromine atoms into organic molecules. The two reactions are similar as both require an initiator and proceed by a free radical chain reaction. This similarity does not hold for the reactions in which the bromination by *N*-bromosuccinimide proceeds by an ionic mechanism, *e.g.*, the nuclear bromination of aromatic compounds.

Subsequent publications will extend this reaction to the introduction of acyloxy and imido groups:

$$\left.\begin{matrix}\text{POOH}\\ \text{or}\\ \text{POOP}'\end{matrix}\right\rangle + \text{RH} + \left\langle\begin{matrix}\text{POOH}\longrightarrow\\ \text{R}'\text{CO}_2\text{H}\longrightarrow\\ \text{R}'\text{NHR}''\longrightarrow\end{matrix}\right.$$

$$\begin{matrix}\text{POOR} + \text{POH} + \text{H}_2\text{O (or P}'\text{OH)}\\ \text{R}'\text{CO}_2\text{R} + \text{POH} + \text{H}_2\text{O (P}'\text{OH)}\\ \text{R}'\text{R}''\text{NR} + \text{POH} + \text{H}_2\text{O (or P}'\text{OH)}\end{matrix}$$

All of these reactions are promoted by copper salts, but most of them occur, to some extent, even in their absence. This study deals with reactions where the main function of the metal salts is only to initiate the decomposition of the hydroperoxides. Subsequent publications will discuss reactions where the metal salts also react with the free radicals initially formed, to alter the course of the reaction.

It has been previously shown that:

(*a*) If reactive free radicals are generated in a solution of *tert*-butyl hydroperoxide in cumene, *tert*-butyl-α-cumyl peroxide is formed. The free radicals were generated by the termal decomposition of acetylperoxide.[5a]

(*b*) Cobalt salts catalyze the decomposition of hydroperoxides, causing the formation of reactive free radicals.[5b]

(*c*) In the presence of a reactive substrate like cyclohexene[5c] or tetralin,[5d] cobalt salts catalyze the reaction of the hydroperoxides with the substrate to form peroxides.

The present work indicates that by careful choice of the catalyst and the reaction conditions, these reactions can be made very general and almost quantitative.

(1) Previous communication, M. S. Kharasch and A. Fono, *J. Org. Chem.*, 23, 324 (1958).

(2) This work was made possible through the generous support of O. B. May, Inc. Newark, N. J.

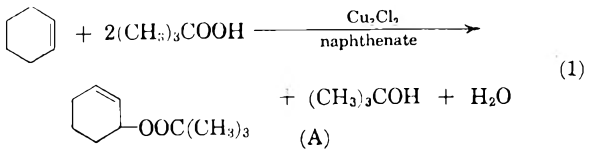
(3) Deceased.

(4) Present address: Firestone Chemical and Physical Research Laboratories, Akron, Ohio.

(5) (a) M. S. Kharasch, A. Fono, and W. Nudenberg, *J. Org. Chem.*, 15, 753 (1950). (b) M. S. Kharasch, A. Fono, W. Nudenberg, and B. Bischof, *J. Org. Chem.*, 17, 207 (1952). (c) M. S. Kharasch, P. Pauson, and W. Nudenberg, *J. Org. Chem.*, 18, 322 (1953). (d) W. Treibs and G. Pellmann, *Ber.*, 87, 1201 (1954).

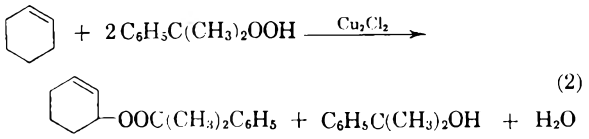
RESULTS

Reaction of tert-butyl hydroperoxide and α-cumyl hydroperoxide with cyclohexene in the presence of cuprous chloride. It was shown that, in the presence of small amounts of cobaltous naphthenate, *tert*-butyl hydroperoxide reacts with cyclohexene, or with octene-1 to give unsymmetrical peroxides.[5c] The yield of 1-*tert*-butylperoxycyclohexene (A), on the basis of the hydroperoxide used was approximately 60%. Much of the hydroperoxide decomposed by chain reaction into oxygen and *tert*-butyl alcohol. Present work indicates that the amount of oxygen liberated in the reaction may be considerably decreased by adding the cobalt salt very slowly. The hydroperoxide is used more efficiently in the presence of cuprous chloride.



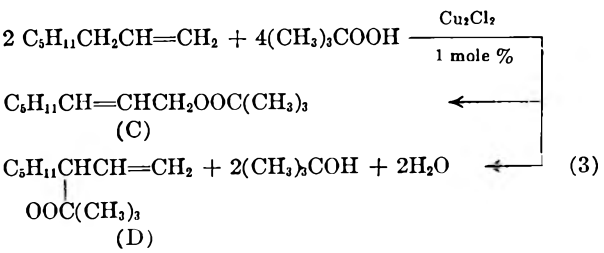
(1)

When 1 mole % of cuprous chloride was added to a mixture of cyclohexene and α-cumyl hydroperoxide (on the basis of the peroxide used), and this mixture kept at 70° for 20 hr., the yield of the unsymmetrical peroxide B was nearly quantitative. This peroxide is quite stable and may be distilled without decomposition at reduced pressure (90°/0.1 mm.). Based on infrared spectrum, analysis, and anology, structure B is suggested.



(2)

Reaction of tert-butyl hydroperoxide with octene-1 in the presence of cuprous chloride. When a mixture of *tert*-butyl hydroperoxide and octene-1 is heated at 75° for 14 hr., only a small amount of the hydroperoxide was decomposed. However, in the presence of one mole % of cuprous chloride, 80% of the hydroperoxide was decomposed at 70° in 6 hr. The reaction products were *tert*-butyl alcohol and about equal quantities of C and D, 1-*tert*-butylperoxyoctene-2 and 3-*tert*-butylperoxyoctene-1, respectively. The same reaction occurred when instead of a copper salt, a cobalt salt was used as a catalyst.



(3)

When to a mixture of *tert*-butyl hydroperoxide and octene-1 very small amounts (0.2 mole %) of cobalt-2-ethylhexoate (dissolved in octene-1) were added at 65–70° over a period of 2 hr., peroxides C and D were again formed in equal quantities. The fractions containing a mixture of peroxides C and D obtained from the copper and the cobalt salt catalyzed reactions were identical with each other in all physical properties (index of refraction, boiling point and infrared spectrum).[6]

Peroxides C and D, the components of the reaction mixture were separated by distillation, using a Piros-Glover spinning band column. The fractions to which structures D and C were assigned boiled at 57°/2.5 mm. (n_D^{20} 1.4243), and 72°/2.5 mm. (n_D^{20} 1.4320) respectively. The infrared spectrum of C with a band at 970 cm.$^{-1}$,[7] indicated the presence of a nonterminal (*trans*) bond. The infrared spectrum of D (bands at 920 cm.$^{-1}$ and 990 cm.$^{-1}$) indicates the presence of a terminal double bond.[8] The infrared spectra of C and D suggest that they probably do not contain more than 5% of each other. A 50–50 mixture of C and D showed an identical infrared spectrum with the crude peroxide isolated from the reaction.

Reaction of tert-butyl hydroperoxide with cumene in the presence of cuprous salts. A solution of *tert*-butyl hydroperoxide in cumene is stable when heated to 70° for 24 hr. However, if 1 mole % of cuprous chloride is added to this solution, and the combined mixture heated to 67° for 18 hr., about 80% of the hydroperoxide is decomposed, according to the stoichiometric reaction 4.

(4)

The *tert*-butyl-α-cumyl peroxide E obtained has the same physical constants (b.p. 60°/2 mm.; n_D^{20} 1.4800) as the *tert*-butyl-α-cumyl peroxide prepared from either *tert*-butyl hydroperoxide and dimethylphenylcarbinol (α-cumyl alcohol),[9] or from cumene, *tert*-butyl hydroperoxide, and acetyl peroxide.[10]

Cupric chloride, cuprous and cupric bromide, cuprous and cupric benzoate were found to be just as effective catalysts as cuprous chloride.

(6) The apparent difference in the abundance of the isomers of C and D observed here, and by Kharasch, Pauson, and Nudenberg [*J. Org. Chem.*, 18, 322 (1953)] is to be ascribed to the fact that better fractionating columns are now in use.

(7) There is an additional strong band at 1017 cm.$^{-1}$

(8) Note that a similar shift of the band from 910 cm.$^{-1}$ to 920 cm.$^{-1}$ was noted in the infrared spectrum of 3-bromooctene-1 [M. S. Kharasch, R. Malec, and N. C. Yang, *J. Org. Chem.*, 22, 1443 (1957)].

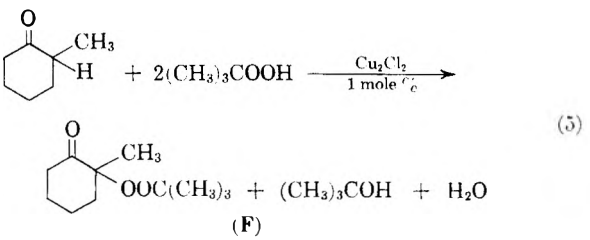
(9) M. S. Kharasch, A. Fono, W. Nudenberg, and A. C. Poshkus, *J. Org. Chem.*, 15, 775 (1950).

(10) M. S. Kharasch, A. Fono, and W. Nudenberg, *J. Org. Chem.*, 15, 753 (1950).

The same peroxide was also obtained, when instead of excess cumene, benzene or chloroform, or heptane or *tert*-butyl alcohol, or pyridine, or acetic acid, or nitrobenzene, or ethyl acetate was used as a solvent. These solvents were also found to be suitable for the preparation of the other peroxides reported here.

A good yield of *tert*-butyl-α-cumyl peroxide E was also obtained by heating a mixture of cumene, *tert*-butyl hydroperoxide, and cobalt 2-ethylhexoate (0.2 mole %) to 65–70°. The cobalt salt was dissolved in cumene and added, drop by drop, over a period of 3 hr. The only difference noted when cobalt salts were used instead of cuprous salts, was the formation of large amounts (30%) of dimethylphenylcarbinol.[11] The best yield, 92%, of pure *tert*-butyl-α-cumyl peroxide was obtained when acetic acid was used as a solvent, and manganous bromide was substituted for the cuprous or cobaltous salt.

Reactions of 2-methylcyclohexanone and of cyclohexanone with tert-butyl hydroperoxide in the presence of cuprous salts. A mixture of 2.5 moles of 2-methylcyclohexanone, 1 mole of *tert*-butyl hydroperoxide, and 1 mole % of cuprous chloride was heated to 60° for 7 hr. 75% of the hydroperoxide had decomposed at the end of that time, and a practically quantitative yield of the unsymmetrical peroxide, on the basis of the hydroperoxide consumed, was obtained. Based on infrared spectrum, analysis, and anology, structure F is suggested.



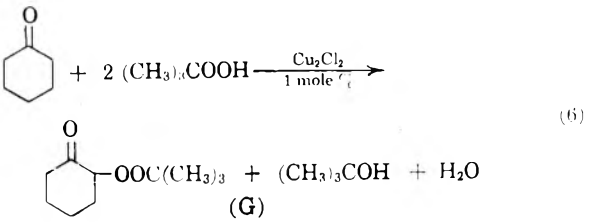
(5)

(F)

The infrared spectrum of 2-methyl-2-*tert*-butylperoxycyclohexanone (F) showed bands in the carbonyl region at 1722–1725 cm.$^{-1}$ 2-methylcyclohexanone has a band at 1705–1710 cm.$^{-1}$ The shift was attributed to the presence of an electro negative substituent in the 2 position. Compound F also had bands at 1370 cm.$^{-1}$ (strong) and 1390 cm.$^{-1}$ (medium) which indicated the presence of a *tert*-butyl group. Bands at 1198 cm.$^{-1}$ and 888 cm.$^{-1}$ were attributed to the presence of the *tert*-butoxy group.

(11) The nonformation of *tert*-butyl-α-cumyl peroxide in the experiment described by Kharasch, Pauson, and Nudenberg,[4] is attributed to comparatively large quantities of the cobalt naphthenate used. When this, or cobalt-2-ethylhexoate is used as a reagent, it is important that small amounts of a dilute solution of the cobalt salt be added gradually over a 2- to 4-hr. period to obtain satisfactory yields. This procedure eliminates the evolution of oxygen which takes place in the presence of more concentrated solutions of cobalt salts.

In the presence of 1 mole % cuprous chloride, the reaction of cyclohexanone with *tert*-butyl hydroperoxide gave many products: adipic acid, the half-aldehyde of adipic acid, and approximately 20% of the unsymmetrical peroxide, 2-*tert*-butylperoxycyclohexanone (G). Left to stand, peroxide G slowly decomposes. Therefore, we felt it plausible to assume that G is a primary reaction product and that other compounds arose from the thermal decomposition of G, in the presence of the *tert*-butyl hydroperoxide and the cuprous (or cupric) salt.



(6)

(G)

An infrared spectrum of a freshly prepared sample of G shows bands at 1368 cm.$^{-1}$ (strong) and 1390 cm.$^{-1}$ (medium), indicating the presence of the *tert*-butyl group. Bands at 875 cm.$^{-1}$ (medium) and 1200 cm.$^{-1}$ (medium) are attributed to the presence of the *tert*-butoxy group. A band at 1720 cm.$^{-1}$ (strong) is accredited to the carbonyl group. Note the shift caused by an α substituent. Cyclohexanone has a band in the carbonyl region at 1710 cm.$^{-1}$ The same shift in wave length has been observed in cyclohexanones halogenated in the 2-position.

Reactions of dimethylaniline with tert-butyl hydroperoxide in the presence of cuprous salts. Because it is a strong base, several attempts to attack dimethylaniline by free radicals have failed. It can be brominated by *N*-bromosuccinimid, giving *p*-bromodimethylaniline in 75% yields.[12] However, it has been shown[13] that this is an ionic and not a free radical reaction. When benzoyl peroxide was decomposed in dimethylaniline,[14] the product *o,o'*-bis(dimethylamino)diphenyl amine again seemingly arose through an ionic mechanism. The reaction was not influenced by the presence of copper salts. Nitrogen is known to activate a neighboring carbon-hydrogen bond[15] and we expected that free radicals should preferentially attack the methyl groups of dimethylaniline.

When we added 1 mole % cuprous chloride to an equimolar mixture of dimethylaniline and *tert*-butyl hydroperoxide dissolved in benzene, the reaction mixture proceeded to heat up. It was maintained at 35°. After 12 hr., the iodometric titer in acidic acid dropped to one half of its original value. From the reaction mixture, we were able to isolate

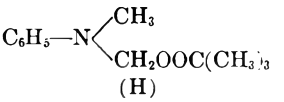
(12) Ng. Ph. Buu-Hoï, *Ann.*, **556**, 1 (1944).

(13) Robert Malec, Ph.D. thesis, University of Chicago, 1957.

(14) L. Horner and E. Schenk, *Ann.*, **566**, 69 (1950).

(15) W. H. Urry, O. O. Juveland, and F. W. Stacey, *J. Am. Chem. Soc.*, **74**, 6155 (1952).

N-methyl-*N*-*tert*-butylperoxymethylaniline (H) in yields in excess of 90%.

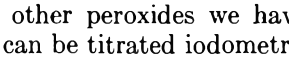


(H) (7)

Similar to other compounds containing a *tert*-butylperoxy group, the infrared spectrum of Compound H has bands at 1370 cm.$^{-1}$ (strong) and 1390 cm.$^{-1}$ (medium) indicating the presence of *tert*-butoxy groups. Below 880 cm.$^{-1}$ the spectrum is almost identical with that of dimethylaniline (no nuclear substitution).

Unlike the other peroxides we have described, compound H can be titrated iodometrically in acetic acid. It is soluble in hydrochloric acid. It is astonishingly stable. Its titer dropped only 5% after 24 hr. refluxing in benzene. With prolonged treatment with acids, it can be hydrolyzed to monomethylaniline.

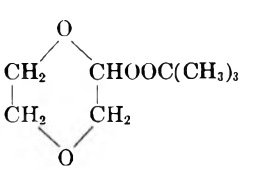
Reaction of p-xylene with tert-butyl hydroperoxide in the presence of cuprous salts. *p*-Xylene is expected to be more susceptible to free radical substitution reactions than cumene, which yields a weak radical. This shall be discussed in detail in a future publication. However, the expected peroxide was of interest to us as the preparation of a hydroperoxide from *p*-xylene is known to give very low yields.[16] The *p*-methylbenzyl *tert*-butyl peroxide (J) was prepared in the usual manner with 85% yield.



(I) (8)

The infrared spectrum indicated the presence of all the bands characteristic for a *tert*-butoxy group.

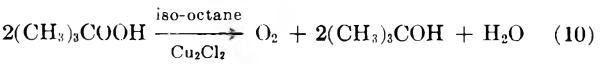
Reaction of dioxane 1,4 with tert-butyl hydroperoxide in the presence of cuprous salts. The previous reactons indicated that in these substitution reactions, the peroxy group can substitute slightly activated primary, secondary, and tertiary hydrogens; that the activating group can be an aromatic ring, a double bond, a keto group, or a nitrogen atom. We prepared the peroxide of dioxane to show that an oxygen atom can also act as an activating group. We also wished to prepare a peroxide which is somewhat water soluble. Compound K, 2-*tert*-butylperoxy dioxane 1,4 was prepared in the usual manner and purified by chromatography. The yield was 50%.



(K) (9)

After 1 week at 0°, the infrared spectrum indicated no decomposition. Preliminary tests indicated that peroxide K can be decomposed by heat without exploding.

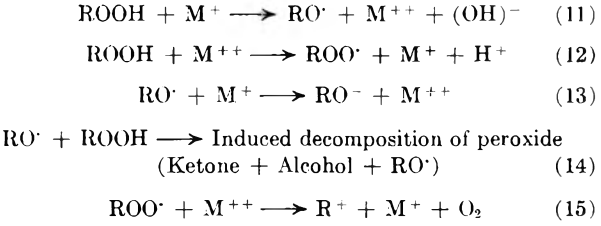
Decomposition of tert-butyl hydroperoxide in iso-octane in the presence of cuprous chloride. Although a solution of *tert*-butyl hydroperoxide in iso-octane is stable when heated to 67°, the addition of 1 mole % of cuprous chloride to the hydroperoxide caused decomposition in approximately 20 min. The reaction is:



(10)

DISCUSSION

First let us discuss the decomposition of *tert*-hydroperoxides into oxygen and alcohols using metal salts, which act as both oxidants and reductants. The following chain mechanism has been suggested.[17]



(11)

(12)

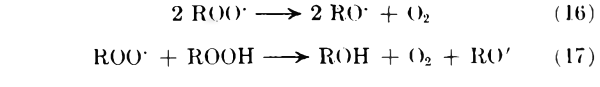
(13)

(14)

(15)

The intermediate formation of a carbonium ion (Equation 15) could not be substantiated. Carbonium ions react with hydroperoxides to give peroxides (10), and if the reaction is carried out in acetic acid, as a solvent, they should form acetates. Increasing the concentration of the hydroperoxides leads however, to less and not more peroxide formation. Similarly, in acetic acid as a solvent, only traces of acetate are formed.

The oxygen evolution has to derive either from the interaction of 2 peroxy radicals (Equation 16) or from the reaction of a peroxy radical with a hydroperoxide (Equation 17).



(16)

(17)

At a higher hydroperoxide concentration, products start to appear, which obviously derive from the RO. radical. A definite proof has to come from studies with O^{18}.

Direct evidence of the existence of RO· radicals (Equation 11) has been obtained by running this reaction in water at 0°, in the presence of butadiene and using a large amount of ferrous salts.[18] The RO· radicals are picked up by the butadiene, and the radical formed dimerizes:

(16) H. Hock and S. Lang, *Ber.*, **76**, 169 (1943).

(17) M. S. Kharasch, A. Fono, W. Nudenberg, and B. Bischof, *J. Org. Chem.*, **17**, 207, (1952). The present authors never observed the formation of symmetrical peroxides from hydroperoxides, in inert solvent, where acid catalyzed reaction could be excluded.

(18) M. S. Kharasch, F. S. Arimoto, and W. Nudenberg, *J. Org. Chem.*, **16**, 1556, 1951).

$$RO^{\cdot} + H_2C{=}CHCH{=}CH_2 \longrightarrow (ROC_4H_6)^{\cdot} \quad (18)$$

$$2\,(ROC_4H_6)^{\cdot} \longrightarrow (ROCH_2CH{=}CHCH_2{-})_2 \quad (19)$$

The existence of ROO· radicals (Equation 12), as intermediates, was proven by a similar method.[5] Using excess butadiene as a solvent, and cobaltous salts as catalyst, the ROO· radicals are picked up by the butadiene. The resulting radical reacts with another hydroperoxide and a one-electron oxidizing agent to give dialkylperoxy butene:

$$ROO^{\cdot} + H_2C{=}CHCH{=}CH_2 \longrightarrow (ROOC_5H_6)^{\cdot} \quad (20)$$

$$(ROOC_4H_6)^{\cdot} + ROOH + Ox \longrightarrow ROOC_4H_6OOR + H^+ + (Ox + e) \quad (21)$$

Now let us consider the decomposition of hydroperoxides, which leads to the formation of peroxides. The apparent ability of a carbon free radical to react with a hydroperoxide and a 1-electron oxidizing agent simultaneously was demonstrated by isolating *tert*-butyl-α-cumyl peroxide, in good yields, when acetylperoxide was decomposed in cumene, in the presence of *tert*-butyl hydroperoxide.[10] This study suggested the following mechanism for this reaction:

$$(CH_3CO_2)_2 \longrightarrow 2\,CH_3^{\cdot} + 2\,CO_2 \quad (22)$$

$$CH_3^{\cdot} + C_6H_5(CH_3)_2CH \longrightarrow CH_4 + C_6H_5(CH_3)_2C^{\cdot} \quad (23)$$

$$C_6H_5(CH_3)_2C^{\cdot} + ROOH \longrightarrow ROOH{\cdot}C(CH_3)_2C_6H_5 \text{ (Radical complex L)} \quad (24)$$

$$L + Ox \longrightarrow ROOC(CH_3)_2C_6H_5 + (Ox + e) \quad (25)$$

Equation 24 proposes that free radicals can form a radical complex with a hydroperoxide, identical with a radical complex formed from a peroxy radical and a hydrocarbon. Later, Swarz and Smid[19] postulated a radical complex as intermediate, to explain the ability of benzoyloxy radicals, but not of methyl radicals, to abstract a hydrogen from trifluoro acetic acid. Hammond *et al.*[20] were forced to assume that some inhibitors can form loose complexes with radicals. An alternate possibility is that the reaction mixture contains a large concentration of comparatively stable ROO· radicals, and that this comparatively stable radical is capable of picking up all carbon radicals, as they are formed.

The comparatively fast decomposition of *tert*-butyl hydroperoxide in iso-octane indicates that the free radicals initially formed from the hydroperoxide are stabilized in a solvent containing reactive hydrogens. This favors the theory of a radical complex formation. The hydroperoxide is also more stable in aromatic solvents, which are known to stabilize radicals through complex formation.[21]

In subsequent papers, we shall show that radicals can react with benzoic and acetic acids, in the presence of 1-electron oxidizing agents, to give benzoates and acetates. The assumption of a comparatively stable acetoxy radical is incongruent with the known readiness of acetoxy radicals to break down into methyl radicals and carbon dioxide.

We established that metal salts generate both alkoxy (RO·) and alkylperoxy (ROO·) radicals from hydroperoxides; Further, that carbon free radicals are capable of reacting with hydroperoxides and a 1-electron oxidizing agent to form peroxides. The following mechanism is suggested for the metal salt catalyzed formation of a peroxide from an organic molecule, containing a slightly activated hydrogen a hydroperoxide.

$$ROOH + M^+ \longrightarrow RO^{\cdot} + M^{++} + OH^- \quad (26)$$

(M is Cu, Mn, or Co^+)

$$RO^{\cdot} + R'H \longrightarrow ROH + R'^{\cdot} \quad (27)$$

$$R'^{\cdot} + ROOH \longrightarrow R'{\cdot}HOOR \quad (28)$$

$$ROOH + M^{++} \longrightarrow ROO^{\cdot} + M^+ + H^+ \quad (29)$$

$$ROO' + R'H \longrightarrow R'{\cdot}HOOR \quad (30)$$

$$R'{\cdot}HOOR + Ox \longrightarrow R'OOR + (Ox + e) + H^+ \quad (31)$$

(The oxidant can be either Me^{++} or a hydroperoxide.)

The reaction between *tert*-butyl hydroperoxide and octene-1 gave both 1-*tert*-butylperoxyoctene-2, and 3 *tert*-butylperoxyoctene-1. An alternate mechanism for the formation of peroxides from an olefin, where the initial step is the addition of a peroxyradical to the double bond, must be rejected. (*cf.* 5c).

Another alternate mechanism to avoid the necessity of having to postulate a radical complex would be:

$$R'^{\cdot} + Ox \longrightarrow R'^{+} + (Ox + e) \quad (32)$$

$$R'^{+} + ROOH \longrightarrow R'OOR + H^+ \quad (33)$$

This mechanism would predict that if the reaction is carried out in the presence of an excess of acetic acid, an appreciable amount of acetate should be formed. However, when *tert*-butyl hydroperoxide was decomposed by metal salts, in the presence of cumene in acetic acid as solvent, α-cumyl *tert*-butyl peroxide was still isolated in 92% yield. Therefore, reactions 32 and 33 do not occur. In subsequent papers, it will be shown that the acetates can be prepared by homolytic mechanism, but that they form only if the acetic acid present in the formation is kept to a low concentration. This is a requirement, which we will show, favors the homolytic mechanism.

The reactions described in this study do occur, to some extent, in the absence of metal salts. After 24 hr. heating of *tert*-butyl hydroperoxide in cumene at 105°, followed by distillation and chromatography, about 5% α-cumyl-*tert*-butyl peroxide could be isolated. This prompted us to present a mechanism where the only role of the metal salts is to initiate free radical reactions. However, the observation that with copper salts fewer by-products

(19) M. Swarz and I. Smid, *J. Chem. Phys.*, **27**, 421 (1957).

(20) G. S. Hammond, E. E. Boozer, C. E. Hamilton, and J. N. Sen, *J. Am. Chem. Soc.*, **77**,3238 (1955).

(21) G. A. Russel, *J. Am. Chem. Soc.*, **80**, 4987 (1958).

are formed indicates that the metal salts do participate to some extent in these reactions. Their role is to stabilize the intermediate radical complexes. The evidence for this view will be presented in subsequent publications.

EXPERIMENTAL

The reactions we have described were carried out in an atmosphere of nitrogen gas. All of the reagents, with the exception of α-cumyl hydroperoxides were distilled prior to use. The purity of the hydroperoxides used is indicated in the individual experiments. The metal salts used were the ordinary laboratory reagent and unless indicated, were not finely powdered. The rate of the decomposition of the reaction mixture of the hydroperoxides was followed by titration at periodic intervals. The spinning band columns used were of the Piros-Glover type.

Preparation of compound B (α-cumylperoxycyclohexene). A mixture containing cyclohexene (0.9 mole), α-cumyl hydroperoxide (0.11 mole containing 75% of hydroperoxide), and cuprous chloride (0.1 g.) was heated at 70° for 20 hr. At the end of that time, a titration showed that 75% of the hydroperoxide had decomposed. The copper salt was collected on a filter. The volatile materials were removed at a pressure of 16 mm. The unreacted hydroperoxide was removed at 75°/0.1 mm. The residue (9 g.) was distilled at reduced pressure (98°/0.1 mm., n_D^{20} 1.5238). The yield of peroxide B was 90% on the basis of the hydroperoxide used.

Anal. Calcd. for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68; mol. wt. 232. Found: C, 77.8; H, 8.8; mol. wt. 220.

The infrared spectrum and the amount of unsaturation were in agreement with the proposed structure.

Preparation of compounds C and D. (C) $C_5H_{11}CH{=}CHCH_2OOC(CH_3)_3$; (D) $C_5H_{11}CHCH{=}CH_2OOC(CH_3)_3$.

(*a*) A mixture of octene-1 (0.35 mole), *tert*-butyl hydroperoxide (0.09 mole: 10 g. of 80% material), and cuprous chloride (0.1 g.) was heated to and maintained at 70° for 7 hr. At the end of that time, a titration showed that 80% of the hydroperoxide had been consumed. The copper salt was collected on a filter, while the low boiling materials in the filtrate were removed at 16-mm. pressure. The residue (7.6 g.) was distilled at reduced pressure. The material boiling at 37–42°/0.1 mm. was collected (6 g.: n_D^{20} 1.4290). This material was a mixture of compounds C and D. The yield, on the basis of the hydroperoxide consumed in the reaction was 85%. The infrared spectrum of this mixture indicated that it contained a small amount, less than 5% of an α,β unsaturated aldehyde (octenal).

Anal. Calcd. for $C_{12}H_{24}O_2$: C, 71.95; H, 12.08; mol. wt. 200. Found: C, 72.3; H, 12.2; mol. wt. 190.

The material that boiled at 37–42°/0.1 mm. was carefully fractionated, using a spinning band column. We removed 10% of the total mixture, boiling at 42–56°/2.5 mm. It consisted of octenal and some of compound D. Two main fractions were obtained:

Fraction 1. 2.5 g. Compound D, b.p. 57°/2.5 mm.; n_D^{20} 1.4243.

Anal. Calcd. for $C_{12}H_{24}O_2$: C, 71.95; H, 12.08. Found: C, 72.0; H, 12.2.

Fraction 2. 2.6 g. Compound C, b.p. 72°/2.5 mm.; n_D^{20} 1.4320.

Anal. Calcd. for $C_{12}H_{24}O_2$: C, 71.95; H, 12.08. Found: C, 72.0; H, 11.9.

(*b*) The reaction described in (*a*) was repeated. In place of cuprous chloride, a 0.5% solution of cobalt 2-ethylhexoate in octene-1 (0.2 mole %) was added dropwise, over a period of 3 hr. At the end of that time, approximately 80% of the hydroperoxide had been consumed. A small amount of alumina was added and the solid collected on a filter. The filtrate was worked up in the same manner as described in section (*a*). The yield and the physical constants of compounds C and D were the same as described in section (*a*).

Preparation of compound E (tert-butyl-α-cumyl peroxide). (*a*) A mixture containing cumene (0.62 mole), *tert*-butyl hydroperoxide (0.29 mole containing 80% of a hydroperoxide), and cuprous chloride (0.2 g.) was heated at 67° for 18 hr. At the end of that time, a titration showed that 80% of the hydroperoxide had decomposed. The copper salt was collected on a filter. The volatile materials were removed at a pressure of 12 mm. A residue (24 g.) contained approximately 80–85% of compound E and approximately 15% of a mixture of acetophenone and dimethylphenylcarbinol (cumyl alcohol). The mixture was separated by distillation through a fractionating column. The pure peroxide E (60%) distilled at 60°/2 mm., n_D^{20} 1.4800.

Anal. Calcd. for $C_{12}H_{20}O_2$: C, 74.95; H, 9.7. Found: C, 74.80; H, 10.0.

The infrared spectrum of the compound E obtained in this manner was identical with the spectrum of *tert*-butyl-α-cumyl-peroxide prepared from dimethylphenylcarbinol and *tert*-butyl hydroperoxide.[9]

(*b*) The experiment just described was repeated. In place of cuprous chloride, a solution (0.5%) of cobalt 2-ethyl hexoate in cumene (0.2 mole %) was added dropwise during a period of 3 hr. At the end of that time, approximately 80% of the hydroperoxide had been consumed. A small amount of alumina was added, the mixture was shaken, and the solid collected on a filter. The low boiling materials were removed from the filtrate by distillation. An attempt to separate the residue by distillation through a spinning band was unsuccessful. This was attributed to the presence of considerable quantities of dimethylphenylcarbinol, which boiled at approximately the same temperature as the unsymmetrical peroxide. The pure peroxide E (n_D^{20} 1.4790) was obtained by chromatographic separation on alumina, using petroleum ether as the eluent. The yield of the unsymmetrical peroxide was 60%. The yield of the dimethylphenylcarbinol was approximately 30%.

A much higher yield (90%) of *tert*-butyl-α-cumyl peroxide was obtained when this same reaction was carried out at 100–110°. At that temperature, only a minute amount (0.05 mole %) of cobalt 2-ethyl hexoate was added. The reaction was usually complete in 30 min.

(*c*) A mixture containing cumene (0.4 mole), acetic acid (0.84 mole), *tert*-butyl hydroperoxide (0.14 mole, containing 85% of hydroperoxide), and manganous bromide (0.0006 mole; 4 mole % on the basis of the hydroperoxide used) was heated at 80° for 11 hr. At the end of that time, titration showed that 86% of the hydroperoxide had decomposed. The reaction mixture was poured into water and the layers separated. The organic layer was dried and distilled. The material which boiled at 50°/20 mm. was collected. Almost all of the residue distilled at 45°/0.15 mm. Ninety-two per cent of this material (n_D^{20} 1.4820) was *tert*-butyl-α-cumyl peroxide containing a minute amount of acetophenone (n_D^{20} 1.5338). The index of refraction of the pure *tert*-butyl-α-cumyl peroxide is n_D^{20} 1.4790–1.4800. A very satisfactory yield of *tert*-butyl-α-cumyl peroxide was obtained when cuprous salt was substituted for the manganese salt in the experiment just described.

Preparation of compound F (2-methyl-2-tert-butylperoxycyclohexanone). A mixture consisting of 2-methylcyclohexanone (0.52 mole), *tert*-butyl hydroperoxide (0.19 mole containing 80% hydroperoxide), and cuprous chloride (0.1 g.) was heated at 60° for 7 hr. At the end of that time, a titration indicated that 75% of the hydroperoxide had reacted. The copper salt was collected on a filter. The low boiling materials were removed from the filtrate by distillation at 12 mm. The residue (13.5 g.) was practically pure peroxide F (95%). Distillation of this material through a column (b.p. 66°/2 mm.; n_D^{20} 1.4431) gave the pure peroxide F in over 90% yield.

Anal. Calcd. for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07; mol. wt. 200. Found: C, 65.9; H, 9.9; mol. wt. 189.

Preparation of compound G (2-tert-butylperoxycyclohexanone). A mixture consisting of cyclohexanone (0.61

mole), *tert*-butyl hydroperoxide (0.2 mole containing 90% of hydroperoxide), and cuprous chloride (0.1 g.) was heated at 92° for 8 hr. At the end of that time, a titration showed that 90% of the hydroperoxide had decomposed. The copper salt was collected on a filter. The volatile material was removed from the filtrate at a pressure of 12 mm. The residue, 12 g., was dissolved in hot benzene. Cooling produced a solid (3 g.) which was separated and collected on a filter. The solid material melted at 151–152° and did not depress the melting point of an authentic sample of adipic acid. The benzene was removed from the filtrate and the residue subjected to distillation. A fraction (4 g.) boiling at 52°/0.15 mm. was collected, leaving a residue I (5 g.). The distillate still contained a small amount of an acidic impurity. To remove it, the distillate was dissolved in benzene, and then washed with a water solution of sodium carbonate. The benzene was then removed at reduced pressure leaving an oil (n_D^{20} 1.4500) which was assumed to be compound G.

Preparation of compound H (N-methyl-N tert-butylperoxymethylaniline). A mixture containing dimethylaniline (0.19 mole), *tert*-butyl hydroperoxide (0.39 mole), cuprous chloride (0.0003 mole), and benzene (1.6 mole) was maintained at 35° for 12 hr. At the end of that time, iodometric titration indicated the loss of 50% of the active oxygen. Some neutral alumina was added, and filtered. The benzene and *tert*-butyl alcohol formed were distilled off *in vacuo*. The crude peroxide was purified by chromatographic separation through a short column of neutral alumina, using petroleum ether as the eluent. Small amounts of amine oxides were formed as by-products. The purified peroxide, b.p. 75°/0.1 mm., n_D^{20} 1.5160, was obtained in over 90% yield. It can be titrated iodometrically in acetic acid. It is soluble in dilute aqueous hydrochloric acid and its titer dropped only 5% after refluxing for 24 hr. in benzene.

Anal. Calcd. for $C_{12}H_{19}O_2N$: C, 68.86; H, 9.15; N, 6.70; mol. wt. 209. Found: C, 69.1; H, 8.9; N, 7.0; mol. wt. 212.

Comparison of its infrared spectrum to that of dimethylaniline indicated no additional substitution in the aromatic ring. After prolonged warming in aqueous hydrochloric acid, monomethylaniline was isolated.

Preparation of compound J (p-methylbenzyl tert-butyl peroxide). A mixture consisting of *p*-xylene (1.0 mole), *tert*-butyl hydroperoxide (0.26 mole), and cuprous chloride (0.1 gram) was heated to 50° and maintained at that temperature for 10 hr. At the end of that time, titration showed that 50% of the hydroperoxide had been consumed. The lower boiling materials were removed *in vacuo*. The crude peroxide was purified by a chromatographic separation through a short column of neutral alumina, using petroleum ether as an eluent. The yield was 0.55 mole (85%) on the basis of the hydroperoxide that was decomposed. The by-product was *p*-methylbenzaldehyde. The peroxide J is a pleasant smelling liquid, b.p. 65°/0.2 mm., n_D^{20} 1.4858.

Anal. Calcd. for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34; mol. wt. 194. Found: C, 74.40; H, 9.17; mol. wt. 186.

The infrared spectrum of the peroxide J had bands at 1360 cm.$^{-1}$ (strong) and 1385 cm.$^{-1}$ (medium), which indicated the presence of a *tert*-butyl group. The bands at 1190 cm.$^{-1}$ and 875 cm.$^{-1}$ are ascribed to the presence of the *tert*-butoxy group.

Preparation of compound K (tert-butylperoxydioxane 1,4). A mixture containing *tert*-butyl hydroperoxide (0.22 mole), dioxane 1,4 (1.00 mole), and cuprous chloride (0.05 g.) was heated to 70° and maintained at that temperature for 12 hr. At the end of that time, titration showed that 85% of the hydroperoxide had been consumed. The lower boiling materials were removed *in vacuo*. The infrared spectrum of the crude reaction product indicated strong keto and hydroxy bands. The peroxide was purified by chromatographic separation through a short neutral alumina column, using petroleum ether as an eluent. Yield of the peroxide K was 0.095 mole (50% on the basis of the hydroperoxide consumed).

The *tert*-butyl peroxy dioxane 1,4, b.p. 55°/0.25 mm., n_D^{20} 1.4325 is somewhat soluble in water. Its infrared spectrum contains bands at 1360 cm.$^{-1}$ (strong) and 1390 cm.$^{-1}$ (medium) indicating the presence of a *tert*-butyl group. The bands at 1185 cm.$^{-1}$ and 875 cm.$^{-1}$ are given to the presence of the *tert*-butoxy group.

Anal. Calcd. for $C_8H_{16}O_4$: C, 54.53; H, 9.15; mol. wt. 176. Found: C, 54.32; H, 8.93; mol. wt. 176.

Decomposition of tert-butyl hydroperoxide in iso-octane. A mixture containing *tert*-butyl hydroperoxide (0.1 mole), iso-octane (0.4 mole), and cuprous chloride (1 g.) was heated to 67°. A violent reaction followed. Within 20 min., all of the hydroxyperoxide decomposed and oxygen gas (0.5 mole) had evolved. The react on mixture did not react with dinitrophenyl hydrazine (no ketones), nor with concentrated HI (no peroxides).

CHICAGO, ILL.

[CONTRIBUTION FROM THE DEPARTMENT OF INDUSTRIAL CHEMISTRY, THE FACULTY OF ENGINEERING, KYOTO UNIVERSITY]

Kinetics and Mechanism of the Perkin Reaction

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The condensation of benzaldehyde with acetic anhydride to yield cinnamic acid, using various basic catalysts such as triethyl-, tripropyl-, tributyl-, and triisobutylamine, has been studied kinetically at 125–155° in kerosine as solvent. The rate of the formation of cinnamic acid as well as that of the disappearance of benzaldehyde has been followed by ultraviolet spectrophotometry. The rate was found to be expressed as k(benzaldehyde) (acetic anhydride) in an excess of the catalyst, while as k(benzaldehyde) (catalyst) in an excess of acetic anhydride. The variation of the rates with changing catalysts was shown to be ascribed to the variation of both frequency factor and energy of activation. A precise fit to the Hammett equation was observed with substituted benzaldehydes, with a positive ρ value of 2.25 at 135°. A mechanism involving a rate-determining attack of a complex of acetic anhydride with trialkylamine [$Ac_2O.R_3N$] on the carbonyl carbon of benzaldehyde is presented and discussed.

Although the Perkin reaction has long been studied as a problem of organic chemistry,[1] only a few kinetic and mechanistic studies[2] have so far been reported. Buckles and Bremer[2b] followed the triethylamine-catalyzed reaction of benzaldehyde and phenylacetic acid by estimating a reactant (benz-

(1) For the review see, J. R. Johnson, *Org. Reactions*, I, 248 (1942).

aldehyde) and using an unsatisfactory rate equation.[3] Therefore, it seems of value to examine the reaction mechanism in detail.

It is now generally accepted that base-catalyzed condensations of carbonyl compounds with active-hydrogen compounds, *e.g.*, Claisen condensation, involve a preliminary equilibrium of proton elimination giving carbanion, followed by the condensation. It is expected that the Perkin reaction also occurs by this mechanism,[2b,c] but little is known regarding the rate-determining step and the attacking agent.

The purpose of the present investigation was to elucidate the mechanism of the reaction from the kinetic order with respect to acetic anhydride and base (trialkylamines) and from the effect of structural changes in the bases together with the effect of substituents in benzaldehyde on the rate.

Results. Table I summarizes data on the initial rates v_0 of the triethylamine-catalyzed condensation

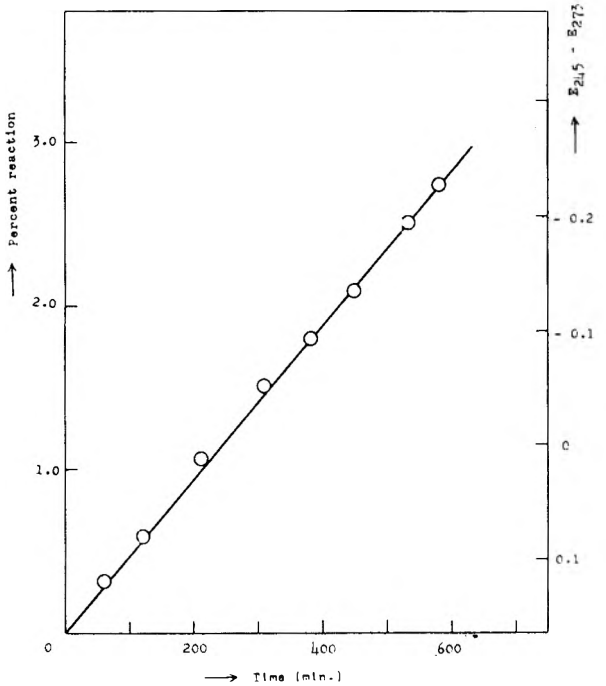

Fig. 1. A typical run for rate measurement. Initial concentrations: benzaldehyde 1.396*M*, acetic anhydride 1.136*M*, triethylamine 0.808*M*

(2) (a) D. S. Breslow and C. R. Hauser, *J. Am. Chem. Soc.*, **61**, 786 (1939); (b) R. E. Buckles and K. G. Bremer, *J. Am. Chem. Soc.*, **75**, 1487 (1953); (c) L. P. Hammett, *Physical Organic Chemistry*, McGraw-Hill Book Co., New York, N. Y., 1940, p. 345.

(3) Their equation should read

$$v = k\,[C_6H_5CHO]\,[C_6H_5CH_2COOH]\,[CH_3COO^-]/[CH_3COOH]^2$$

although their equation is valid provided that $[C_6H_5CH_2COOH]$ in the equation means the stoichiometric concentration of phenylacetic acid.

(4) R. Livingston, *Investigation of Rates and Mechanism of Reactions*, (*Technique of Organic Chemistry*, Vol. VIII), S. L. Friess and A. Weissberger, ed., Interscience, New York, N. Y., 1953, p. 182.

TABLE I

RATE OF CONDENSATION OF BENZALDEHYDE WITH ACETIC ANHYDRIDE IN KEROSINE AT 135 ± 0.5° WITH TRIETHYLAMINE CATALYST

	Initial Concentration[a]			Initial Rate,
	$Et_3N(m)$ M	$Ac_2O(a)$ M	BzH(b) M	$v_0 \times 10^7$, Mole L.$^{-1}$ Sec.$^{-1}$
(A)	0.808	1.986	1.396	9.97
	0.808	1.702	1.396	10.53
	0.808	1.419	1.396	10.39
	0.808	1.136	1.396	10.61
	0.606	1.419	1.396	7.63
	0.606	1.136	1.396	7.70
	0.606	0.851	1.396	7.54
(B)	0.808	1.419	1.703	12.91
	0.808	1.419	1.396	10.39
	0.808	1.419	1.118	7.98
	0.808	1.419	0.838	6.10
	0.808	1.419	0.698	5.14
	0 808	1.419	0.599	4.33
(C)	0.808	1.419	1.396	10.39
	0.606	1.419	1.396	7.62
	0.467	1.419	1.396	6.01
	0.404	1.419	1.396	4.74
	0.351	1.419	1.396	4.52
	0.301	1.419	1.396	3.68
(D)	1.010	1.136	1.396	9.54
	1.010	0.851	1.396	7.07
	1.010	0.712	1.396	5.95
	1.010	0.612	1.396	4.97
	1.010	0.566	1.396	4.63
	1.010	0.450	1.396	3.56
(E)	1.010	1.136	1.703	11.48
	1.010	1.136	1.396	9.54
	1.010	1.136	1.118	7.63
	1.010	1.136	0.838	5.69
	1.010	1.136	0.698	4.62
	1.010	1.136	0.599	3.83
(F)	1.212	0.851	1.396	6.55
	1.010	0.851	1.396	7.08
	0.808	0.851	1.396	6.60
	1.212	0.566	1.396	4.62
	1.010	0.566	1 396	4.63
	0.808	0.566	1.396	4.79

[a] $fa > m$ in the case of (A), (B) and (C), while $fa < m$ in the case of (D), (E), and (F).

of benzaldehyde with acetic anhydride in kerosine with varying molar ratio of each reactant and catalyst. The v_0 value was obtained graphically.[4] A typical run is shown in Fig. 1.

It will be seen from the table that the initial rates are proportional to benzaldehyde and that they are also proportional to both acetic anhydride and triethylamine provided that their concentrations are not large, but the linearity departs and the rate becomes almost independent of the excess reagent.

Table II lists the initial rates of the condensation of benzaldehyde with acetic anhydride in kerosine using various catalysts, *i.e.*, triethylamine, tripropylamine, tributylamine, and triisobutylamine. The variation of the rates with temperature is also recorded in Table II together with the calculated energies of activation and frequency factors.

Table III shows the effect of para substituents in benzaldehyde on the rate with triethylamine catalyst. It is apparent that the effect of the substituents on the rate constant satisfies the Hammett equation (Fig. 2), giving a ρ value of +2.25.

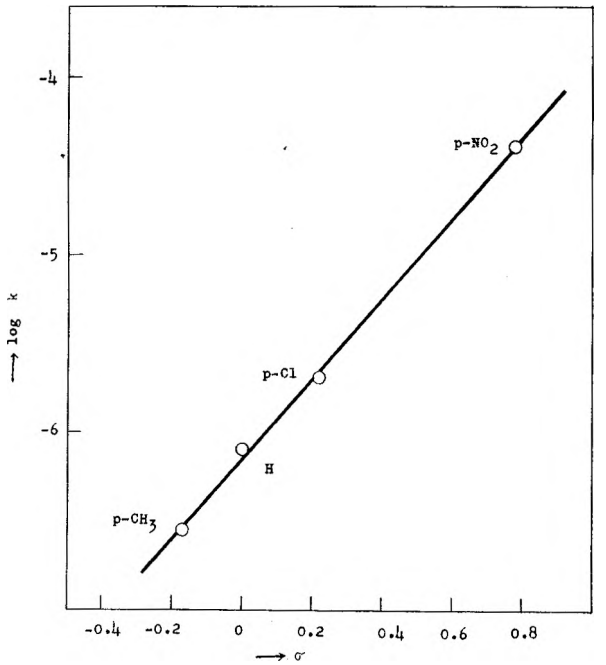

Fig. 2. The Hammett's relationship for the triethylamine-catalyzed condensation of benzaldehydes with acetic anhydride in kerosine at 135° (ρ = +2.25)

Discussion. The above facts seem to imply the presence of a complex[5] consisting of triethylamine and acetic anhydride as an attacking agent instead of a simple conjugate base of acetic anhydride as suggested in the Claisen condensation.[2c,6] Thus an excess reagent will take little part in the rate-determining step. The observed rate dependence upon benzaldehyde in Table I together with a high positive ρ value (+2.25) suggests that the rate-determining attack of the above complex occurs on the positive carbonyl carbon of benzaldehyde

$$Ac_2O + NEt_3 \underset{K}{\overset{\text{fast}}{\rightleftharpoons}} CH_3COOCOCH_2 \cdots H{-}\overset{+}{N}Et_3 \quad (1)$$

$$Ph{-}\underset{-O}{\overset{H}{C}}{}^{+} + \overset{\bar{C}H_2COOCOCH_3}{H} \xrightarrow[k]{\text{slow}} Ph{-}\underset{-O}{\overset{H}{C}}{-}CH_2COOCOCH_3 + \overset{+}{N}HEt_3 \quad (2)$$

$$Ph{-}\underset{-O}{\overset{H}{C}}{-}CH_2COOCOCH_3 \xrightarrow{\text{fast}} Ph{-}CH{=}CH{-}COOH + CH_3CO\bar{O} \quad (3)$$

where K and k denote equilibrium constant and rate constant of the steps 1 and 2, respectively.

Provided that the rate of reaction 2 is negligible in calculating the concentration of complex p, the initial stoichiometric concentrations of acetic anhydride and triethylamine m are related by

$$K = \frac{p}{(fa - p)(m - p)} \quad (4)$$

where f is a correction factor for the concentration of acetic anhydride, the meaning of which, however, is still obscure. If the initial concentration of acetic anhydride is much larger than that of tri ethylamine, *i.e.*, $fa >> m$. it follows that $(fa - p)$ approximates to fa, since p cannot exceed m; thus Equation 4 is simplified to

$$K = \frac{p}{fa(m - p)} \quad (5)$$

or

$$p = \frac{fKam}{fKa + 1} \quad (6)$$

Thence the initial rate v_0 is expressed approximately as follows:

$$v_0 = kpb = \frac{kfKamb}{fKa + 1} \quad (7)$$

where b denotes the initial concentration of benzaldehyde. If fKa is sufficiently large than unity, the rate may be expressed as follows.

$$v_0 = k\,m\,b \quad (8)$$

Analogously, when $fa << m$, the rate becomes, if mK is larger than unity

$$v_0 = k\,f\,a\,b \quad (9)$$

The results shown in Table I satisfy these relations; *i.e.*, if acetic anhydride is in excess over the amine, the rate varies linearly with concentrations of both benzaldehyde and triethylamine but is independent of acetic anhydride (Eq. 8), and if triethylamine is in excess over the anhydride, linear dependence on both benzaldehyde and acetic anhydride and independence of triethylamine are observed (Eq. 9). These relationships are also shown in Fig. 3. The value of f was calculated from Equations 8 and 9 to be 1/1.395.

With regard to the complex formation, the fact that the very low solubility of acetic anhydride in kerosine is much increased by addition of triethylamine suggests the intimate interaction between both components. Ultraviolet and infrared absorption spectra (Fig. 4) also suggest the complex formation.

It seems of interest to note that the present reaction is somewhat different from the analogous pi-

(5) It is probable, however, that the fact is due to a solvent effect, *i.e.*, this nonpolar solvent may be unable to effect dissociation into $CH_2\bar{C}OOCOCH_3$ and $\overset{+}{N}HEt_3$, which might be conceivable in polar solvents.

(6) A. A. Frost and R. G. Pearson, *Kinetics and Mechanism*, John Wiley & Sons, Inc., New York, N. Y., 1953, p. 208.

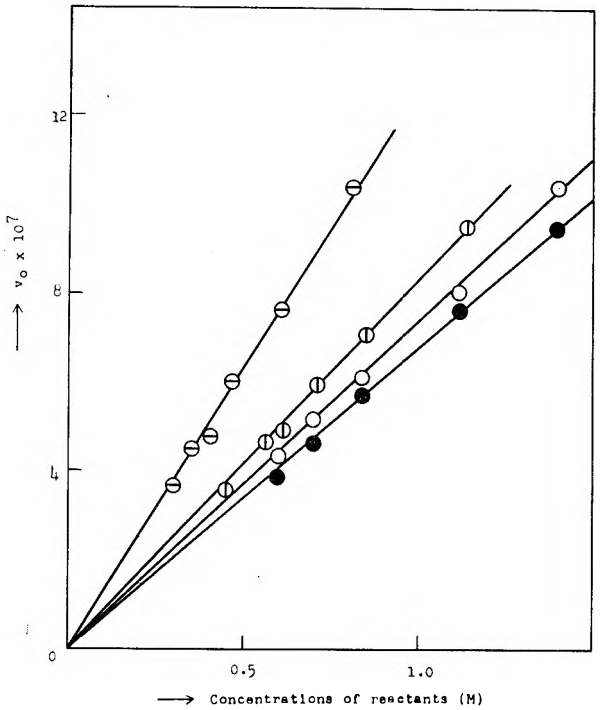

Fig. 3. Plots of initial rates (v_0) against initial concentrations of the reactants (Equation 8 and 9). Data of (B)○, (C)⊖, (D)⊙, and E ● in Table I

peridine-catalyzed condensation of benzaldehyde with diethyl malonate.[7] The addition of a small amount of organic acid greatly increases the rate of the latter reaction, while it has little effect on the present condensation. Moreover, although both electron-releasing and attracting para substituents retard the condensation of benzaldehyde and diethyl malonate, a precise fit to Hammett equation and a high ρ value (+2.25) are observed in the present reaction. Mechanistic difference between the two condensations is thus apparent; it is probable that in the piperidine-catalyzed condensation of benzaldehyde with diethyl malonate a complex consisting of benzaldehyde and piperidine reacts with diethyl malonate, while in the triethylamine-catalyzed condensation of benzaldehyde with acetic anhydride a complex composed of triethylamine and acetic anhydride attacks the positive carbonyl carbon of benzaldehyde.

The effect of catalyst. In spite of the fact that energy of activation is comparable to those of the related reactions, this condensation is considerably slow, owing to the low frequency factors (Table II). The bulkiness of the attacking agent as well as the complex formation, as shown in Equation 1, may explain the low frequency factors. This complex will be favored particularly in nonpolar solvents, and such a polar structure will make the frequency factor especially small in this solvent.[8]

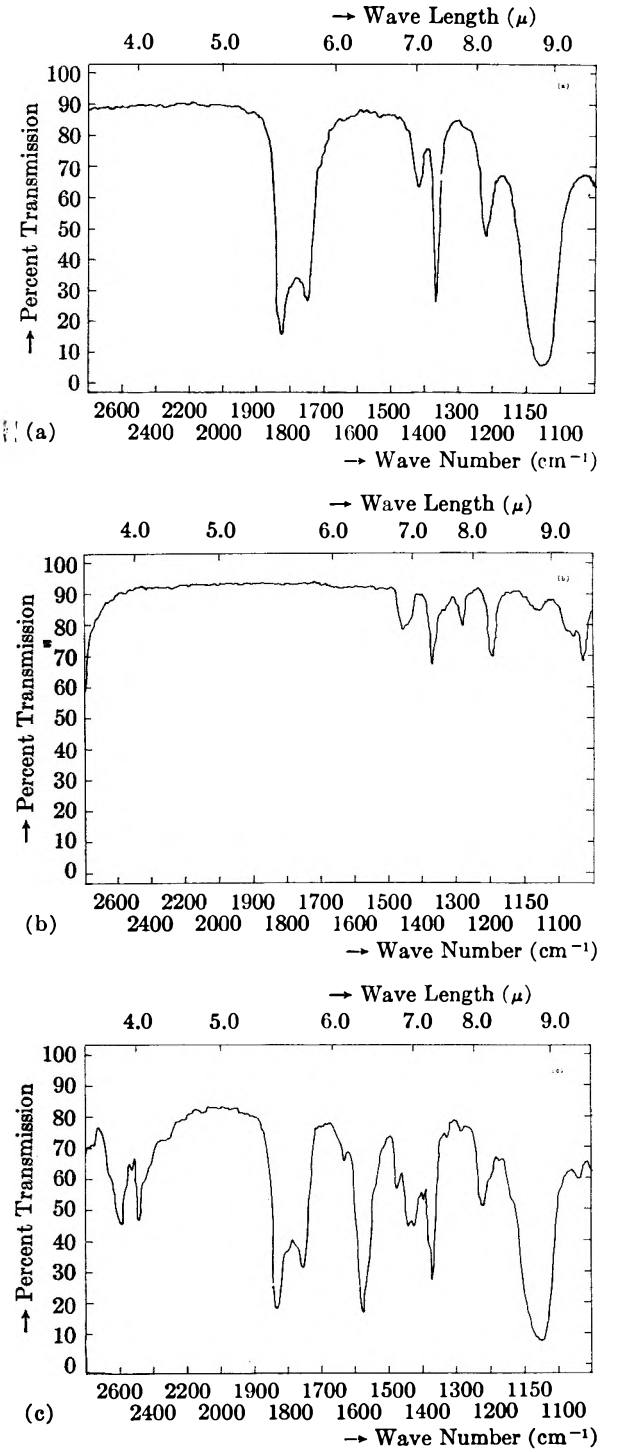

Fig. 4. Infrared absorption spectra of acetic anhydride (a), triethylamine (b), and an equimolar mixture of them (c)

The order of the basicity of trialkylamines (Et_3N < Pr_3N < Bu_3N < i-Bu_3N)[9] is in the reverse order of the catalytic ability of these amines (Et_3N > Bu_3N > Pr_3N >> i-Bu_3N). The fact implies an importance of steric requirements in this reaction. If the conjugate base of acetic anhydride was an at-

(7) Unpublished work.

(8) C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, Cornell University Press, Ithaca, N. Y., 1953, p. 347.

(9) H. Landolt-R. Boernstein, *Phusikalischen Chemische Tabellen*, 5 Auflage, Julius Springer, Berlin, 1936.

TABLE II

EFFECT OF CATALYSTS ON RATE, ENERGY OF ACTIVATION, AND FREQUENCY FACTOR OF THE CONDENSATION OF BENZALDEHYDE WITH ACETIC ANHYDRIDE IN KEROSINE AT VARIOUS TEMPERATURES[a]

Amine	Temp., °C.	$v_0 \times 10^7$ (Mole L.$^{-1}$ Sec.$^{-1}$)	Ea (k_{cal} mole^{-2})	Log PZ
Et_3N	117.5	6.77		
	132.5	9.99		
	135	12.25	10.8	−0.27
	140	13.77		
	135	3.96		
Pr_3N	145	5.63		
	155	7.66	11.4	−0.22
	135	4.61		
Bu_3N	145	6.87		
	155	9.25	12.0	+0.14
	135	0.44[b]		
i-Bu_3N	155	1.14	9.8[b]	−1.62[b]

[a] Initial concentrations: trialkylamine, 1.10M; acetic anhydride, 1.419M; benzaldehyde, 1.396M. [b] The rate was too slow for accurate measurements.

TABLE III

EFFECT OF PARA SUBSTITUENTS ON RATE OF TRIALKYLAMINE-CATALYZED CONDENSATION OF BENZALDEHYDE WITH ACETIC ANHYDRIDE IN KEROSINE AT 135 ± 0.5°[a]

p-Substituent	v_0 (Mole L.$^{-1}$ Sec.$^{-1}$)
CH_3	3.94×10^{-7}
H	1.23×10^{-6}
Cl	2.88×10^{-6}
NO_2	5.73×10^{-5}
$\rho = +2.25$	

[a] Initial concentrations: triethylamine, 1.010M; acetic anhydride, 1.419M; benzaldehydes, 1.396M.

tacking agent, the rate order would be identical to the basicity order. It has been found, however, that the yields of the metallic acetate–catalyzed Perkin reactions of *o*-chlorobenzaldehyde and acetic anhydride at 180° for 8 hr. depend on the metals of the acetate as follows: Li, 58%; Na, 71%; K, 78%; Rb, 82%.[10] The order is consistent with the order of the basicity of the acetate and strongly suggests the importance of the acetate ion concentration in this polar medium.

The effect of substituents. The polar effect of substituents in benzaldehyde (or the Hammett's ρ value) is especially large ($\rho = +2.25$). This will also be an indication of rate-determining combination of strongly polarized reactants as indicated in Equation 2.

EXPERIMENTAL

Materials. Acetic anhydride was purified by double distillation, b.p. 139° (lit.[11] b.p. 139.5°). The triethyl- and tributylamines used were of best grade and purified by careful distillations, b.p. 89° (lit.[12] b.p. 89°) and 215° (lit.[13] b.p. 216.5°), respectively. Propyl and isobutyl bromides were prepared by the reaction of the corresponding alcohols, potassium bromide, and sulfuric acid, which was then heated with ammonia in aqueous methanol. The resulting tripropylamine and triisobutylamine were repeatedly rectified, b.p. 156° (lit.[14] b.p. 156.5°) and 185° (lit.[15] b.p. 185°), respectively.

Commercial benzaldehyde was washed with an aqueous solution of sodium carbonate and then water, dried, and distilled with addition of a small amount of hydroquinone, b.p. 178° (lit.[16] b.p. 178°). *p*-Tolualdehyde was prepared from *p*-xylene by the chromyl chloride oxidation in chloroform[17] and purified by duplicate distillations, b.p. 205° (lit.[17] b.p. 204°). *p*-Chlorobenzaldehyde was prepared from *p*-chlorotoluene *via* *p*-chlorobenzal bromide[18] and purified by recrystallization from aqueous methanol, m.p. 47° (lit.[19] m.p. 47°). *p*-Nitrobenzaldehyde was obtained by the oxidation of *p*-nitrotoluene with chromium trioxide in a mixture of glacial acetic acid and acetic anhydride[20]; yellow needles, m.p. 106° (lit.[20] m.p. 106°).

Cinnamic acid, *p*-nitro-, *p*-chloro-, and *p*-methylcinnamic acids were prepared by the Perkin condensation of the corresponding aldehydes with acetic anhydride, using potassium acetate as a catalyst, and purified by recrystallization from aqueous acetic acid, m.p. 137° (lit.[21] m.p. 137°, 285° (lit.[22] m.p. 286°), 251° (lit.[23] m.p. 250°), and 197° (lit.[24] m.p. 197°), respectively.

Commercial kerosine was treated several times with fuming sulfuric acid, washed with water, and rectified. A fraction boiling between 240 and 280° was collected, which showed no appreciable absorption at 240–290 mμ in a methanolic solution of the experimental concentration.

A typical procedure for the rate measurements. As an example, the rate measurements of triethylamine-catalyzed condensation of benzaldehyde and acetic anhydride is described below. A mixture of definite amounts of benzaldehyde, acetic anhydride, triethylamine, and kerosine (20 ml.) was placed in a 100-ml. three-necked flask fitted with a thermometer, a reflux condenser, and an outlet tube, and immersed in an oil bath thermostated at 138° ± 0.5°. The reaction mixture was shaken vigorously. In general, 3 min. were necessary to establish the temperature equilibrium; hence all kinetic runs were commenced after that interval. At appropriate time intervals aliquots (0.5 ml.) were taken out, being poured into a 25-ml. volumetric flask containing an insufficient amount of methanol, and diluted accurately to 25 ml. The solution (0.2 ml.) was then diluted to 10 ml. with acidic methanol (5 ml. of concentrated sulfuric acid in 1 l. of methanol), the optical density of the resulting solution being measured at appropriate wave lengths, as indicated in Table IV, by a Beckmann spectrophotometer model DU. The per cent compositions of these solutions were determined in the same manner as previously described.[25] These spectrophotometric data are summarized in Table IV.

The optical density of acetic anhydride was negligible at the concentrations of these measurements. The absorption

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(11) D. C. Jones and H. F. Betts, *J. Chem. Soc.*, 1181 (1928).

(12) J. Timmermans, *Chem. Zentr.*, **85**, 619 (1914).

(13) A. Lieben and A. Rossi, *Ann.*, **158**, 172 (1871).

(14) A. Zander, *Ann.*, **214**, 171 (1882).

(15) R. Sachtleben, *Ber.*, **11**, 734 (1878).

(16) F. W. Perkin, *J. Chem. Soc.*, **69**, 1247 (1875).

(17) H. D. Law and F. M. Perkin, *J. Chem. Soc.*, 259 (1907).

(18) *Cf.*, G. H. Coleman and G. E. Honeywell, *Org. Syntheses*, Coll. Vol. II, 89 (1948).

(19) W. L. McEwen, *Org. Syntheses*, Coll. Vol. II, 133 (1948).

(20) S. V. Lieberman and R. Connor, *Org. Syntheses*, Coll. Vol. II, 441 (1948).

(21) J. Kendall, *J. Am. Chem. Soc.*, **36**, 1726 (1914).

(22) P. Pfeiffer and G. Haefelin, *Ber.*, **55**, 1771 (1922).

(23) J. van der Lee, *Rec. trav. chim.*, **45**, 680 (1926).

(24) T. Posner and G. Schreiber, *Ber.*, **57**, 1131 (1924)

(25) Y. Ogata, M. Tsuchida, and Y. Takagi, *J. Am. Chem. Soc.*, **79**, 3397 (1957).

TABLE IV

SPECTROPHOTOMETRIC DATA FOR RATE MEASUREMENTS. OPTICAL DENSITY OF BENZALDEHYDES AND CINNAMIC ACIDS IN ACIDIC METHANOL (5 ML. OF CONCD. SULFURIC ACID IN 1 L. OF METHANOL)[a]

Materials	Concentration, (M) × 10^5	Optical Density at Various Wave Lengths		
		(245 mμ)	(251 mμ)	(273 mμ)
C_6H_5CHO	384	0.802	0.805	0.080
$C_6H_5CH:CHCO_2H$	3.84	0.112	0.175	0.410
		(240 mμ)	(245 mμ)	(278 mμ)
p-$Cl.C_6H_4CHO$	213	1.074	0.972	0.058
p-$Cl.C_6H_4CH:CHCO_2H$	7.10	0.101	0.162	0.876
		(250 mμ)	(265 mμ)	(297.5 mμ)
p-$O_2N.C_6H_4CHO$	19.2	0.608	0.872	0.210
p-$O_2N.C_6H_4CH:CHCO_2H$	9.60	0.144	0.271	0.746
		(255 mμ)	(260 mμ)	(285 mμ)
p-$H_3C.C_6H_4CHO$	250	1.100	1.053	0.140
p-$H_3C.C_6H_4CH:CHCO_2H$	8.33	0.349	0.481	1.002

[a] It was shown that Beer's law was obeyed in these solutions, and that these optical densities were unaltered with the modest variation of the acidity of the solvent.

of trialkylamines used was conveniently eliminated by the addition of a small amount of sulfuric acid as noted previously. Moreover, the addition of sulfuric acid is advantageous, because the absorption of benzaldehydes is markedly reduced, while that of cinnamic acids is almost unchanged; thus it is possible to estimate accurately a small change in the composition of any reaction mixture.

Complementary experiments. Since most of the kinetic runs were followed only up to 2% conversion, some complementary tests seemed necessary in order to ensure the reaction path. It was confirmed in preliminary tests that the reaction followed spectrophotometrically was truly the Perkin reaction and no appreciable side reaction occurred and also that the sulfuric acid in methanol did not cause any oxidation of benzaldehydes. A typical run carried out with the same reaction mixture as in the kinetic experiments up to 30% conversion at 160° shows a satisfactory agreement of the observed reaction course with the calculated one (Fig. 5).

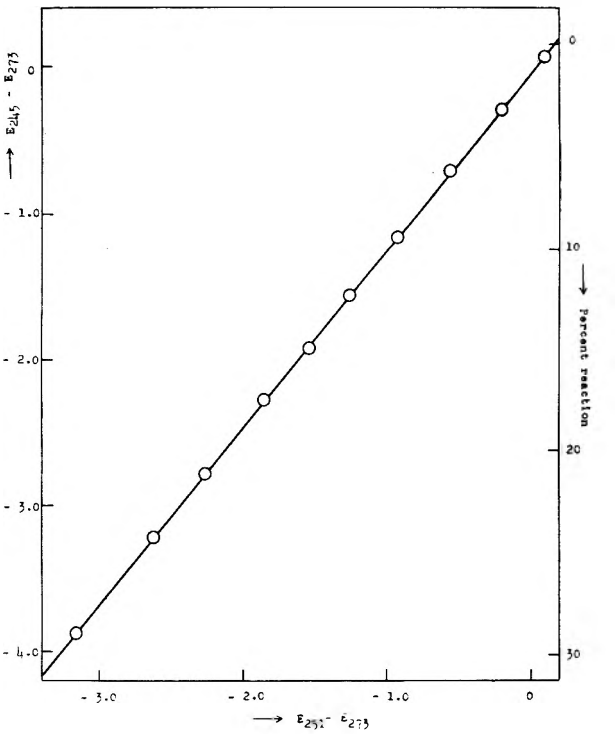

Fig. 5. Agreement of the observed reaction course (circles) with the calculated one (a line). E's are optical densities at the subscripted wave lengths

It was confirmed that no appreciable quantity of acetic acid was produced from the acetic anhydride used, since no kinetic deviation was observed with the same typical runs carried out after three weeks. It is sure also that acetic and cinnamic acids produced during the reaction will have little catalytic effect, since an addition of benzoic acid to the reaction mixture did not change the rate, especially with p-nitrobenzaldehyde, where no effect was observed until separation of the solution into two layers occurred (*ca.* 20% conversion). A report[26] that the effect of the added acid was very small in the base-catalyzed Knoevenagel condensation of cyanoacetic acid with aldehydes at high temperature is consistent with the above observation.

YOSHIDA, KYOTO, JAPAN

(26) M. J. Astle and W. C. Gergel, *J. Org. Chem.*, 21, 493 (1956).

[CONTRIBUTION NO. 75 FROM E. I. DU PONT DE NEMOURS & COMPANY, INC., ELASTOMER CHEMICALS DEPARTMENT]

Chemistry of Aryl Isocyanates: Rate and Equilibrium Constants for the Formation of Ethyl α,γ-Diarylallophanate

I. C. KOGON

Received March 20, 1958

By means of the near infrared spectrum the equilibrium and rate constants for the formation of ethyl α,γ-diarylallophanates from aryl isocyanates and ethyl substituted carbanilates at elevated temperatures have been measured.

In the near infrared region between 14,000 and 4,000 cm.$^{-1}$ are found the absorption bands arising from N—H, C—H and O—H stretching vibrations. In particular, the first overtone of the NH stretching vibration is found near 6750 cm.$^{-1}$ Recently, we have shown that the NH group of ethyl, ethyl-p-methyl and ethyl o-methylcarbanilate exhibit absorption in the region of 6750 cm.$^{-1}$ However, the

NH group of ethyl α,γ-diphenylallophanate does not exhibit this absorption.[1] This absence of absorption is characteristic for this type of structure. This suggests that near infrared spectroscopy can be used to obtain equilibrium and rate data for the formation of ethyl α,γ-diarylallophanate by following the rate of disappearance of carbanilate NH absorption.

Aryl isocyanates react with ethyl carbanilates at 125–140° to give the ethyl α,γ-diarylallophanate.[2] In the presence of a small quantity of a tertiary amine such as *N*-methylmorpholine, the sole product of the reaction is triarylisocyanurate[2] in excellent yield. Evidence that the formation of triarylisocyanurate proceeds through ethyl α,γ-diarylallophanate and aryl isocyanate dimer was presented. Additional evidence for ethyl α,γ-diarylallophanate as one of the intermediates in the reaction is presented in this paper.

EXPERIMENTAL

Materials. Eastman Kodak phenyl isocyanate, *o*- and *p*-tolyl isocyanate were carefully redistilled immediately prior to use. Ethyl alcohol was purified by the method of Fieser.[3]

Ethyl carbanilate and ethyl *o*- and *p*-methylcarbanilate were prepared by a known procedure.[4]

Measurements in 10 cm. cylindrical quartz cells were made with a Cary Model 14 spectrophotometer using a scan speed of 5 mμ per second. The cell holder was thermostatically controlled at 26 ± 0.5°. Redistilled carbon tetrachloride was used as the solvent.

Procedure. The reactants were carefully weighed into a 125 ml. Erlenmeyer flask equipped with a drying tube. The Erlenmeyer and its contents were placed in a constant temperature bath and shaker for 2.5 to 3 min., depending upon the temperature at which the reaction was run. This procedure allowed for the expansion of the reaction mixture. Zero time of reaction was taken immediately after this expansion period. The error involved in this heating period due to reaction between the carbanilate and isocyanate is negligible since the over-all reaction is very slow. At various intervals a 5 ml. aliquot of the solution was quickly removed and dropped into a tared 50 ml. volumetric flask containing 25 ml. of cold carbon tetrachloride (T = 5°). The weight of the 5 ml. aliquot was noted. The solution was allowed to reach room temperature, the volume increased to 50 ml. with additional carbon tetrachloride and the spectrum taken. At room temperature there is no measurable reaction between an aryl isocyanate and ethyl carbanilate. In the concentration range used, the absorbance of radiation at 6750 cm.$^{-1}$ follows the Beer-Lambert law. Aryl isocyanate and ethyl α,γ-diarylallophanate were found to exert no effect on the absorbance of the carbanilates.

The spectra obtained throughout a typical run with ethyl carbanilate and phenyl isocyanate are shown in Fig. 1. Ethyl carbanilate, which exhibits a major band characteristic of the NH group at 6750 cm.$^{-1}$, decreases with time until the equilibrium point is reached.

The calculations for the equilibrium and rate constants are based upon equation (I). The expression for the rate constants was derived on the basis that the forward reaction is pseudo-first order, with the concentration of isocyanate constant.

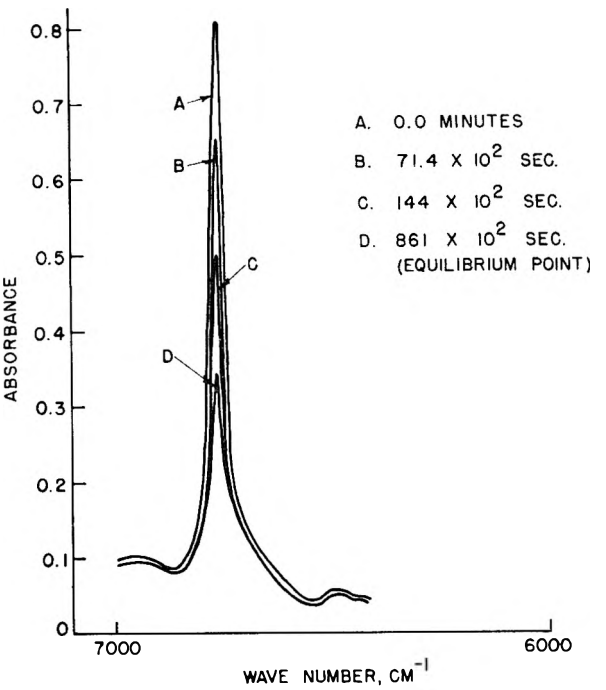

Fig. 1. Near infrared absorption spectra of the reaction of ethyl carbanilate with phenyl isocyanate in the mole ratio of 12:1. Temperature, 128°.

$$\text{Aryl NH—COOC}_2\text{H}_5 + \text{Aryl NCO} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \text{Aryl NHC(=O)—N(Aryl)—COOC}_2\text{H}_5 \quad \text{(I)}$$

In order to simplify our calculations, the trace quantity of aryl isocyanate dimer formed as a by-product of the reaction[2] was assumed to be too small to appreciably affect the calculations of the rate and equilibrium constants. Thus,

$$K_{eq} = \frac{k_1}{k_2} = \frac{X_e}{(u - X)(i - X)}$$

$$k_1 = \frac{2.303}{t(i + 1/K_{eq})} \log \frac{iu}{iu - X(i + 1/K_{eq})}$$

where X = no. of moles of allophanate formed at time t, X_e = no. of moles of allophanate formed at equilibrium, $u - X$ = no. of moles of carbanilate remaining at time t, i = no. of moles of isocyanate initially. The values for the heat and entropy of reaction and the energy of activation were calculated from the equilibrium and rate constants in the usual manner.

Second order rate plots were obtained by plotting log $\frac{iu}{iu - X(i + 1/K_{eq})}$ against time. A typical plot shows the straight line obtained for the phenyl isocyanate/ethyl carbanilate reaction of Fig. 2.

RESULTS AND DISCUSSION

Inspection of the experimental data in Table I, Nos. 3, 5 and 7, shows that the equilibrium constant for the phenyl isocyanate/ethyl carbanilate reaction remains constant at 128° over a concentration range of phenyl isocyanate/ethyl carbanilate of 9.1 to 18.0. An increase in reaction temperature

(1) I. C. Kogon, *J. Am. Chem. Soc.*, 79, 2253 (1957).
(2) I. C. Kogon, *J. Am. Chem. Soc.*, 78, 4911 (1956).
(3) L. Fieser, *Experiments in Organic Chemistry*, D. C. Heath and Co., New York, 1941, p. 358.
(4) H. Vittenet, *Bull. soc. chim. France*, [9] 21, 952 (1899).

TABLE I

RATE AND EQUILIBRIUM CONSTANTS FOR THE REACTION OF ETHYL SUBSTITUTED CARBANILATE WITH ARYL ISOCYANATE

$$RR'C_6H_3NCO + R''R'''C_6H_3N(H)-COOC_2H_5 \rightleftharpoons RR'C_6H_3N(H)-C(=O)-N(C_6H_3R''R''')-COOC_2H_5$$

No.	R	R′	R″	R‴	Temp., °C.	NCO/NH	$K_{equil.}$ Liters/Mole	k × 10^4 Liters/Mole/Sec.	ΔE^a $K_{calcd.}$	ΔH^b $K_{calcd.}$	ΔS^c Calcd./deg.
1	H	H	H	H	137	12.6	0.203	0.065			−13.2
2	H	H	H	H	137	12.6[d]	...	0.072			
3	H	H	H	H	128	12.6	0.242	0.042	15.9	−6.7	−13.8
4	H	H	H	H	128	12.6[d]	...	0.050			
5	H	H	H	H	128	9.1	0.243	0.050			−13.8
6	H	H	H	H	106	12.6	0.397	0.1017	16.5	−6.8	−15.9
7	H	H	H	H	128	18.0	0.248	0.036			−14.0
8	H	H	H	*p*-CH_3	128	12.6	0.349	0.036			
9	H	H	H	*o*-CH_3	128	12.6	0.568	0.127			
10	H	*o*-CH_3	H	*o*-CH_3	143	12.6	0.146	0.070			
11	H	*p*-CH_3	H	*p*-CH_3	143	12.6	0.094	0.043			

[a] Energy of activation. [b] Heat of reaction. [c] Entropy of reaction. [d] Catalyzed by *N*-methyl morpholine.

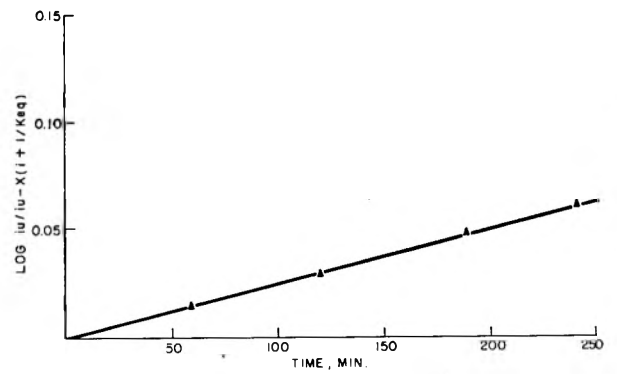

Fig. 2. 2nd Order plot of phenyl isocyanate + ethyl carbanilate. Temp. 137°.

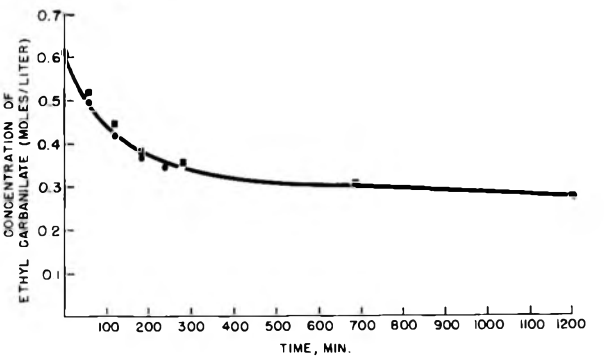

Fig. 3. The rate of disappearance of ethyl carbanilate as followed by the near infrared spectra
■ Uncatalyzed
● Catalyzed with 0.5% *n*-methylmorpholine

from 106° to 137° results in a decrease of the value for K_{eq}. Thus the quantity of ethyl α,γ-diphenylallophanate at *equilibrium* decreases as the temperature increases, (Table I, Nos, 1, 3, 6). This indicates that at the equilibrium point of the reaction a higher yield of ethyl α.γ-diphenylallophanate should be obtained as the temperature is decreased.[5]

The results of the rate measurements given in Table I, (Nos. 3, 8, 9) show that substitution in the *p*-position of the aromatic ring by a methyl group decreases the rate of reaction compared to the unsubstituted and *o*-methyl substituted carbanilate. This is contrary to what we had expected. The mechanism previously proposed for this reaction involved the nucleophilic attack of the carbanilate NH group on the carbon of the isocyanate group followed by a proton shift to give the allophanate.[2] On the basis of this mechanism one would predict that even a weak electron-repelling group such as methyl in the *p*-position of the aromatic ring of the carbanilate should enhance the rate of the forward reaction. However, as Mukaiyanai and Iwanami[6] showed in their thermal decomposition studies of carbanilates at elevated temperatures, benzyl *o*-methylcarbanilate and benzyl carbanilate in the presence of a primary amine, dissociate faster to benzyl alcohol and aryl isocyanate than benzyl *p*-methylcarbanilate. Their mechanism postulates an initial ionization of the carbanilate to the enol anion of the carbanilate followed by dissociation to the substituted benzyl alcohol and aryl isocyanate. Thus, assuming ionization of the carbanilate occurs at elevated temperature the decreased rate of reaction of ethyl *p*-methylcarbanilate with phenyl isocyanate (Table I, No. 8) compared to ethyl carbanilate with phenyl isocyanate (Table I, No. 3) is probably due to retardation of the ionization of the carbanilate to the enol anion by the *p*-methyl group. The greater rate constant for the formation of ethyl α,*o*-tolyl, γ-phenylallophanate (Table I, No. 8) is probably due to steric strain between the *o*-methyl and carbanilate groups of ethyl *o*-methyl-

(5) This has been verified by us and is the subject of another paper.

(6) T. Mukaiyanai and M. Iwanami, *J. Am. Chem. Soc.*, 79, 73 (1957).

carbanilate which results in an increased tendency toward ionization to the enol anion. The enolic form can then react with phenyl isocyanate to give allophanate containing a stable pseudo six-membered ring containing an intramolecular hydrogen bond.[1]

When the aromatic ring of the aryl isocyanate and the ethyl carbanilate both contain a methyl group (Table I, Nos, 10, 11) the rate of reaction of *o*-tolyl isocyanate with ethyl *o*-methylcarbanilate is slightly greater than the rate of reaction of *p*-toly isocyanate with ethyl *p*-methylcarbanilate. Two factors are taken into consideration to account for this enhanced reactivity of the *o*-methyl system; (*a*) effect of the methyl substituent on the aromatic ring of the isocyanate and (*b*) effect of the methyl substituent on the aromatic ring of the carbanilate. It was previously shown that at room temperature *p*-tolyl isocyanate reacts approximately 4 times faster than *o*-tolyl isocyanate toward alcohol or water at 25°.[7] However, as the temperature of the reaction is increased to 100° the relative rates of reaction of the *o*- and *p*-methyl groups begin to approach each other and are different by a factor of approximately 2. On the other hand, as shown above, an *o*-methyl group activates the carbanilate group approximately 3.5 times greater than a *p*-methyl group. Therefore, a larger rate constant should be observed for the formation of allophanate from *o*-tolyl isocyanate with ethyl *o*-methylcarbanilate than from *p*-tolyl isocyanate with ethyl *p*-methylcarbanilate.

The results of the rate measurements for the *N*-methylmorpholine catalyzed reaction of phenyl isocyanate with ethyl carbanilate show that the amine does not have any appreciable catalytic effect on allophanate formation (Table I, Nos, 2 and 4). The spectral data show that carbanilate concentration decreases with time at the same rate as the uncatalyzed reaction (Fig. 3). As the reaction approaches equilibrium a large exotherm occurs followed by solidification of the solution to a mixture of triphenylisocyanurate and ethyl carbanilate. Thus the disappearance of the carbanilate NH absorption band with time indicates that ethyl α,γ-diphenylallophanate is being formed and is an intermediate reaction product in the formation of triphenylisocyanurate from phenyl isocyanate and ethyl carbanilate.

Acknowledgment. The writer wishes to thank Dr. Karl Frensdorff for his aid in deriving the rate equation used in this paper.

WILMINGTON, DEL.

(7) (a) J. Burkus and C. F. Eckert, presented before the Division of Paints and Plastics at the 132nd National Meeting of the American Chemical Society, New York, New York, September 1957. (b) K. C. Smeltz, E. J. Goldberg, I. C. Kogon, W. C. Woodland, Reaction of Water with Isocyanate," submitted for publication.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, FORDHAM UNIVERSITY]

A New Synthesis of 9-Phenanthrol; Absorption Spectra of the Quinhydrone-Type Molecular Compound between 9-Phenanthrol and Phenanthrenequinone

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A new synthesis of 9-phenanthrol from phenanthrene is described in which the novel step is a quantitative pinacol rearrangement of *cis*- or *trans*-9,10-dihydro-9,10-phenanthrenediol. The infrared spectra of 9-phenanthrol shows it to be completely enolized in both the solid state and in solution. Infrared and ultraviolet absorption spectra, combustion analysis, and chromatographic separation support the conclusion that 9-phenanthrol forms a quinhydrone-type molecular compound with phenanthrenequinone in a 1:1 molar ratio.

9-Phenanthrol. 9-Phenanthrol (III), first prepared by Lachowitz[1] *via* 9,10-phenanthrenequinone (I) and 10,10-dichloro-9,10-dihydro-9-phenanthrone, has been of interest because of its conversion in high yields to 9-phenanthrylamine and *N*-alkyl-9-phenanthrylamines (Bucherer reaction) which are structurally related, in at least one important respect, to morphine.[2] III also has marked analgesic properties[3a] and fungi toxicity.[3b]

Improvements in Lachowitz' procedure,[4,5] or alternatively, reduction of I with hydriodic acid and phosphorus,[6,7a] with hydrazine in absolute ethanol[8]

(1) B. Lachowitz, *J. prakt. Chem.*, **28**, 172 (1883); *Ber.*, **17**, 1161 (1883).

(2) L. F. Fieser, R. P. Jacobsen, and C. C. Price, *J. Am. Chem. Soc.*, **58**, 2163 (1936).

(3) (a) N. B. Eddy, *J. Pharmacol. Exptl. Therap.*, **48**, 183 (1933); **51**, 75 (1934). (b) S. Rich and J. G. Horsfall, *Proc. Natl. Acad. Sci. U. S.*, **40**, 139 (1954); *Chem. Abstr.*, **48**, 8831 (1954).

(4) J. Schmitt and H. Lumpp, *Ber.*, **41**, 4215 (1908).

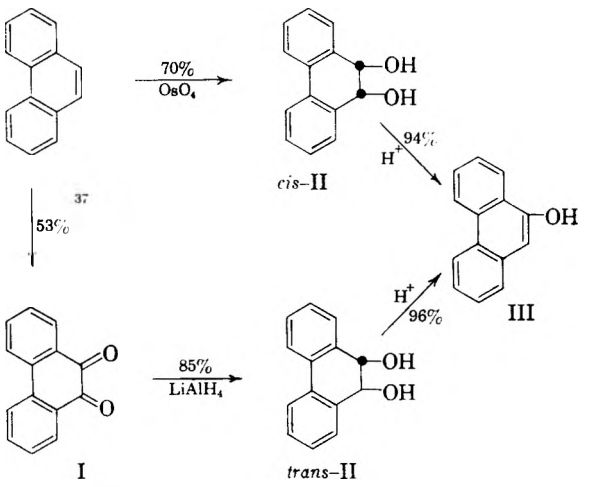
(5) S. Goldschmidt and M. A. Bredig, *Ann.*, **445**, 135 (1925).

(6) F. R. Japp and F. Klingemann, *J. Chem. Soc.*, **63**, 770 (1893).

(7) (a) E. Fourneau and J. Matti, *Bull. soc. chim.*, **7**, 615 (1940). (b) E. Fourneau and J. Matti, *Bull. soc. chim.*, **9**, 633 (1942).

or with hydrogen in the presence of nickel[9] left much to be desired[2] from the viewpoint of yield and procedure.[10] Thereafter three substantially new and direct routes to III were reported: (i) Potassium hydroxide fusion of potassium 9-phenanthrenesulfonate[11] gave III in unreported yields.[16] (ii) Fieser's three-step synthesis from phenanthrene *via* 9-bromo-10-methoxy-9,10-dihydrophenanthrene gave III in 28–30% yields.[2] By this same route, however, Hunsberger, Ketcham, and Gutowsky[17] obtained a 12% yield.[18] In both cases, the yields are based on phenanthrene consumed. (iii) Finally, Schultz, Schultz, and Cochran[19] reported a 5% yield of III in the reaction of fluorenone with two equivalents of diazomethane.[20]

In a previous paper,[22] *cis*- and *trans*-9,10-dihydro-9,10-phenanthrenediols (*cis*- and *trans*-II) were shown to be configurationally related by conversion to the same acid-catalyzed rearrangement product, III.[23] In this paper we wish to report that on the basis of yields and simplicity of procedure, the pinacol rearrangement of *cis*- and *trans*-II diols according to the following scheme seems to be the best available to date for the laboratory preparation of III.



Thus, *cis*-II diol, prepared by an osmium tetroxide hydroxylation of phenanthrene,[22,24] or sodium-amalgam reduction of diphenaldehyde (20%),[22] and *trans*-II diol, obtained by the reduction of I with lithium aluminum hydride[25] or sodium borohydride (70%),[26] can be quantitatively rearranged to III in over-all yields of 66% and 43%, respectively, from phenanthrene. The infrared spectra of III showed a hydroxyl band at 2.76 μ (CCl_4) and at 3.10 μ (Nujol).[27,28] The absence of carbonyl absorption in both the solid state and in solution indicates III to be completely enolized.[17,29]

9-Phenanthrol:Phenanthrenequinone. When wet or in solution, but more slowly in the solid state, III is

(8) S. Dutt and N. K. Sen [*J. Chem. Soc.*, **123**, 3420 (1923)] reported quantitative yields of III from a sealed tube reaction (200°, 6 hr.) between I and hydrazine hydrate in absolute ethanol. However, S. Goldschmidt, A. Vogt, and M. A. Bredig [*Ann.*, **445**, 126 (1925)] showed that under almost identical conditions (sealed tube, 180°, 6 hr.), the product was exclusively tetrabenzo(a,c,h,j)phenazine, and not III. With milder conditions (12-hr. reflux), the Dutt and Sen procedure gave only phenanthrenehydroquinone.

(9) J. von Braun and O. Bayer, *Ber.*, **58**, 2667 (1925).

(10) Worthy of note are the multistep or incidental preparations of III from 9-phenanthrylmagnesium bromide [W. E. Bachmann, *J. Am. Chem. Soc.*, **56**, 1363 (1934)]; from diphenic anhydride [N. Chatterjee, *J. Indian Chem. Soc.*, 12, 410 (1935); *Chem. Abstr.* **30**, 454 (1936)]; from ethyl biphenylyl-2-acetate [R. Sherwood, W. F. Short, and J. Woodcock, *J. Chem. Soc.*, 322, (1936); A. Schönberg and F. L. Warren, *Chem. & Ind. (London)*, **1939**, 199, and Chatterjee (*vide supra*)]; from 9-keto-4b,5,6,7,8,8a,9,10-octahydrophenanthrene [C. D. Gutsche and W. S. Johnson, *J. Am. Chem. Soc.*, **68**, 2239 (1946)]; from phenanthrene [J. W. Cook and R. Schoental, *J. Chem. Soc.*, **47**, (**1950**)]; and from 9-phenoxyphenanthrene [R. L. Huang, *J. Chem. Soc.*, 3295, (1955)].

(11) Prepared in 6%,[12] 7–14.5%,[13] 13%,[14] and 24–30%[15] yields by the sulfonation of phenanthrene.

(12) A. Werner and E. Frey, *Ann.* **321**, 270 (1902).

(13) H. Sandquist, *Ann.*, **392**, 76 (1912).

(14) L. F. Fieser, *J. Am. Chem. Soc.*, **51**, 2460 (1929).

(15) Sister M. G. Solomon and D. J. Hennessy, *J. Org. Chem.*, **22**, 1649 (1957).

(16) A. Werner and E. Frey, *Ann.*, **321**, 299 (1902).

(17) I. M. Hunsberger, R. Ketcham, and H. S. Gutowsky, *J. Am. Chem. Soc.*, **74**, 4839 (1952).

(18) R. P. Linstead, R. R. Whitstone, and P. Levine, *J. Am. Chem. Soc.*, **64**, 2014 (1942) also found that very poor yields were obtained by the Fieser, Jacobsen, and Price procedure *unless* the sodium or potassium acetate was omitted from the reaction mixture.

(19) R. F. Schultz, E. O. Schultz, and J. C. Cochran, *J. Am. Chem. Soc.*, **62**, 2902 (1940).

(20) Other products isolated and identified and their yields, were: 30% 9-methoxyphenanthrene,[21] 1.5% di-9-phenanthryl ether, and 30% unchanged fluorenone.

(21) Using this procedure, Hunsberger, Ketcham, and Gutowsky[17] obtained a 36% yield of 9-methoxyphenanthrene.

(22) E. J. Moriconi, F. T. Wallenberger, L. P. Kuhn, and W. F. O'Connor, *J. Org. Chem.*, **22**, 1651 (1957).

(23) Named 9,10-dihydro-9-phenanthrone in ref. 22 by analogy to the other phenanthrones reported therein.

(24) R. Criegee, B. Marchand, and H. Wannowius, *Ann.*, **550**, 99(1942).

(25) J. Booth, E. Boyland, and E. E. Turner, *J. Chem. Soc.*, 1188, 2808 (1950).

(26) Sodium trimethoxyborohydride reduction gave a negligible amount of *trans*-II diol and a small amount of phenanthrenehydroquinone isolated as the corresponding quinhydrone. See Experimental section.

(27) Hunsberger, Ketcham, and Gutowsky[17] report a hydroxyl band at 2.77μ (CCl_4) and 3.06μ (Nujol).

(28) Infrared spectra by Mr. Joseph Tesar.

(29) Although III is tautomeric with its keto form, 9,10-dihydro-9-phenanthrone, it exhibits no ketone reactions under normal conditions.[30,31a] *Cf.* the transannular tautomerism of 9-anthrol (89%) $\rightleftarrows$ anthrone (11%) in methanol [K. H. Meyer, *Ann.*, **379**, 37 (1911)]; although both forms can be isolated and the substance reacts in either form depending on conditions, the keto form is the more stable. In acetic acid, the equilibrium concentration of anthrone is 98.7%.[31b]

(30) F. R. Japp and A. Findlay, *J. Chem. Soc.*, **71**, 1115 (1897). See ref. 33 for reported exceptions.

(31) (a) S. Coffey and J. Van Alphen in E. H. Rodd's *Chemistry of Carbon Compounds*, Vol. III[b], Elsevier Publishing Co., D. Van Nostrand Co., Inc., New York, 1956, p. 1436. (b) *Ibid.*, p. 1383.

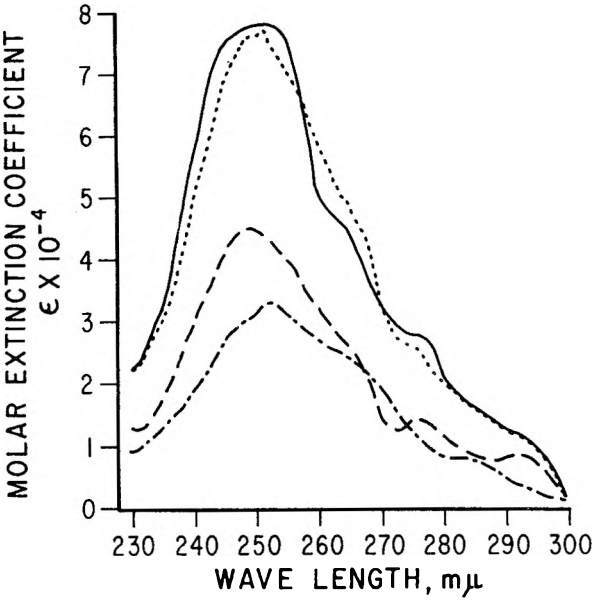
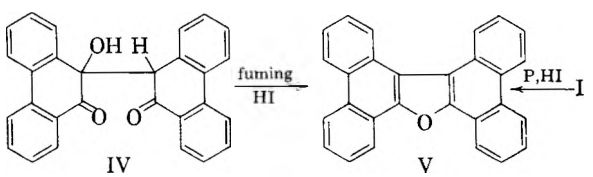


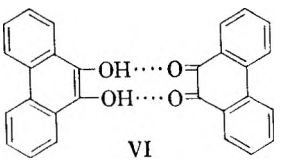
Fig. 1. Ultraviolet spectra of: 9-phenanthrol (III) - - - -; phenanthrenequinone (I) —·—; 9-phenanthrol:phenanthrenequinone molecular compound (VII) —; Molecular compound calculated by addition of component spectra ....

oxidized by air to a dark red, crystalline solid, $C_{28}H_{18}O_3$, m.p., 156–157°. The $C_{28}H_{18}O_3$ compound can also be obtained by simply mixing equimolecular proportions of I and III.[8,30] On reaction, $C_{28}H_{18}O_3$ gave I and 9-phenanthryl acetate with acetic anhydride,[30] I with chromic acid,[31a] and diphenanthro(9,10-*b*,9′,10′-*d*]furane (V) with fuming hydriodic acid[6,30,32] or hydriodic acid with red phosphorus.[8] V could also be obtained by a similar reduction of I with hydriodic acid.[6,30] On the basis of these reactions, Japp and Findlay[30] suggested IV, an aldol condensation product of III (acting in the keto form) and I,[33] both as the structure of $C_{28}H_{18}O_3$ and as the intermediate in the reduction of I to V.



IV V

Alternatively, it has been suggested that $C_{28}H_{18}O_3$ is an impure quinhydrone-type molecular compound between I and phenanthrenehydroquinone (oxidation product of III)[31a] of probable structure VI, analogous to that proposed between I and 10-amino-9-phenanthrol.[34]



VI

Using Japp and Findlay's procedure,[30] we have prepared the $C_{28}H_{18}O_3$ compound from I and III. Combustion analyses showed a 1:1 molar ratio. Its infrared spectrum (CS_2) is virtually a superimposition of the absorption spectra of the pure components I and III (Table I). The ultraviolet absorption spectra (ethanol) of the $C_{28}H_{18}O_3$ compound, the pure components I and III, and the calculated curve by adding the molar extinction coefficients of I and III are shown in Fig. 1. The spectrum of the $C_{28}H_{18}O_3$ compound nearly equals the sum of the

TABLE I

COMPARISON OF INFRARED ABSORPTION BANDS[a] AND INTENSITIES[b] OF PHENANTHRENEQUINONE (I), 9-PHENANTHROL (III), AND MOLECULAR COMPOUND (VII) COMPOSED OF I AND III IN 1:1 MOLE RATIO

Wave Length, Microns		
Phenanthrenequinone (I)	9-Phenanthrol (III)	Molecular compound (VII)
	2.79 m (OH)	2.81 w (OH)
3.28[e]	3.26 w	3.26 w
5.93 s (C=O)		5.93 s (C=O)
	6.12 m	6.13 w
7.52 w	7.58 m	7.58 w
7.80 s		7.81 s
8.17 m		8.17[c]
	8.26 s	8.26 m
	8.57 w	8.60 vw
	8.73 m	8.74 w
8.94 w		8.95 w
	9.02 m	9.03 w
	9.34 s	9.35 m
	9.64 m	9.65 w
9.88 w		9.88 w
10.42 vw		10.42 vw
	10.54 w	10.55 vw
	10.65 w	10.65 vw
10.85 m		10.85 m
	11.67 w[d]	11.66 vw[d]
	12.09 s	12.10 m
	13.10 s	13.10[c]
13.17 s		13.17 s

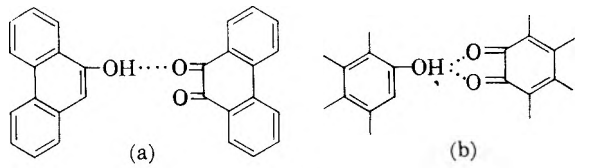
[a] Concn. in CS_2: I and III, 0.02*M*; VII, 0.005*M*; the solubility of VII seems to depend on the rate of dissociation into its compounds I and III with increasing dilution. [b] Band intensities are reported according to the suggestion of H. M. Randall, N. Fuson, R. G. Fowler, and J. R. Dangl, *Infrared Determination of Organic Structures*, D. Van Nostrand Co., Inc., New York, 1949, p. 20: strong (s) = bands of the same order of intensity as the strongest band in the entire spectrum; moderate (m) = bands of $^1/_3$ to $^2/_3$ as intense as the strongest band; weak (w) = bands $^1/_4$ to $^1/_2$ as intense; very weak (vw) = bands of less than $^1/_4$ intensity. Thus for pure components I and III, band intensities are directly comparable. For less soluble VII, the actual concentration of its components I and III is considerably less, and band absorption intensities appearing in VII should be weaker in some cases than identical bands in the spectra of the pure components. [c] Shoulder. [d] Broad band. [e] Inflection.

(32) F. R. Japp and F. Klingemann, *J. Chem. Soc.*, 57, 663 (1890).

(33) This was one of the two instances noted by these authors[30] in which III behaved as a ketone. The second example was the reaction of III with phenylhydrazine at 200° with the elimination of water and ammonia to form an indole derivative. In both cases, they noted that under the vigorous conditions employed, these reactions proved little of the structure of $C_{28}H_{18}O_3$.

(34) G. M. Jaffe and A. R. Day, *J. Org. Chem.*, 8, 43 (1943).

components. Finally, we have separated the components of the $C_{28}H_{18}O_3$ compound by chromatography on an alumina column. Thus the analytical and absorption data support our belief that the $C_{28}H_{18}O_3$ compound is neither IV nor VI but is an intermolecularly, hydrogen-bonded molecular compound of probable structure VIIa, or VIIb (bifurcated hydrogen bond), which is completely dissociated into its components in very dilute solution.



VII

EXPERIMENTAL

All melting points are uncorrected. The infrared spectra were determined with a Model 21 Perkin-Elmer recording spectrometer with NaCl optics. The ultraviolet spectra were observed in a Beckmann quartz spectrophotometer Model DU using 1 cm. quartz cells. The reported ϵ values are for concentrations ranging from 0.00500 g./l. to 0.00250 g./l. in absolute ethanol. Microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

cis-9,10-Dihydro-9,10-phenanthrenediol (*cis*-II). Purified phenanthrene, m.p. 98–98.5°[35] (0.705 g, 3.96 mmoles), was added to a solution of 1.010 g. (3.97 mmoles) of osmium tetroxide in 15 ml. of thiophene-free benzene. The orange solution turned yellow on further addition of 1 ml. of pyridine. On standing 5 days at room temperature, the dark brown crystals of the adduct were filtered off and the filtrate evaporated to dryness. The combined solid residues were dissolved in 50 ml. methylene chloride to which was added a solution of 10 g. mannitol and 1 g. potassium hydroxide in 100 ml. water. The mixture was mechanically shaken until the methylene chloride layer was colorless. If solid material (crude diol) appeared, it was filtered off, and the methylene chloride layer of the filtrate was separated and evaporated to dryness to yield the larger portion of crude diol. The combined pale green residues were recrystallized once from toluene (charcoal) to yield 0.588 g. (2.77 mmole, 70%) of fine, white silky needles, m.p. 179–180°; lit. m.p. 177–178°.[24]

trans-9,10-Dihydro-9,10-phenanthrenediol (*trans*-II) as white, fine silky needles from cyclohexane, m.p. 185–187°[22,25] was obtained in 85% yield[36] from the lithium aluminum hydride reduction of I, and in 70% yield using sodium borohydride according to the following procedure: Dried I,[37] 0.520 g. (2.50 mmoles), was extracted for 12 hr. in a Soxhlet extractor with 150 ml. of carefully dried anhydrous ether containing 0.150 g. (4.00 mmoles) of sodium borohydride, after which the complex was decomposed by adding 20–30 ml. of *N* sulfuric acid in portions to the cooled solution. The flask was carefully swirled to avoid a possible vigorous reaction of the unreacted hydride. The ether layer was separated and the aqueous layer extracted with an additional 50 ml. of ether. The combined ether extracts were washed with *N* sodium hydroxide solution and any insoluble material removed by filtration. The ether solution then was evaporated to dryness. The crude diol (0.420 g.) on recrystallization from benzene and then from cyclohexane gave 0.370 g. (70%) of the *trans*-II diol, m.p. 184–185°.

Reduction of I *with sodium trimethoxyborohydride.* I (0.52 g., 2.5 mmoles) was extracted for 12 hr. in a Soxhlet with 200 ml. of anhydrous ether containing 0.64 g. (5.0 mmoles) of sodium trimethoxyborohydride. The color of the resulting solution was bluish green. The complex was decomposed by the same acid treatment described in the sodium borohydride reduction. Treatment of the combined ethereal extracts with 30–40 ml. of *N* NaOH, precipitated a considerable amount of dark brown material. This was filtered, washed with water, and thrice recrystallized from benzene to yield dark purple-brown flakes, m.p. 169–171°, of phenanthrenequinhydrone (VI),[26] lit. m.p. 167°[7b]; 165–169°.[38]

Anal. Calcd. for $C_{28}H_{19}O_4$: C, 80.37; H, 4.34; Mol. wt., 418. Found: C, 80.52; H, 4.59; Mol. wt., 203 (Rast camphor).[39]

Unreacted I and negligible amounts of *trans*-II diol were recovered from the ether layer. It is of experimental value to note the color changes of the ethereal solution of I with different reductants. With lithium aluminum hydride and sodium borohydride, the solution turned from yellow to colorless, while with sodium trimethoxyborohydride, the color change was from yellow to bluish green.

9-Phenanthrol (III). Conc. sulfuric acid (0.05 ml.) was added to a hot (100–110°) solution of *cis*- or *trans*-II diol, (0.500 g., 2.47 mmoles) in 5 ml. glacial acetic acid. The color of the solution changed from yellow to pink and gradually to orange. After about 10 min. heating the solution was rapidly cooled to room temperature by the addition of small pieces of ice during which time the crude III simultaneously precipitated. The white solid was filtered off and air dried to yield approximately 0.5 g. of crude III. The crude material turned pink immediately after separation from the acetic-sulfuric acid solution and darkened further on air drying on the filter paper. One recrystallization from methanol gave 0.450 g. (2.32 mmoles., 94% yield) from the *cis*-II diol and 0.460 g. (2.37 mmoles., 96% yield) from *trans*-II diol of cream colored III, m.p. 149–150°, lit. m.p. 149–152.1°.[17] The color of the methanolic solution remained yellow in air and III in methanol was far less susceptible to air oxidation than in the original acetic-sulfuric acid solution in which the rearrangement was carried out. III can be stored under nitrogen at 0° for at least several months before it darkens. A spectral sample of III, m.p. 156–157°, was prepared by vacuum sublimation of the recrystallized product at 135–140° and 1–3 mm.

Anal. Calcd. for $C_{14}H_{10}O$: C, 86.57; H, 5.19. Found: C, 86.55; H, 5.21.

Molecular compound between I *and* III (VII). Equimolar amounts of I and III were dissolved in excess, warm anhydrous benzene. The cooled solution was permitted to evaporate slowly to dryness in air. The brown-to-red colored residue (m.p. range, 120–130°) was twice recrystallized from

(35) Bachmann's [*J. Am. Chem. Soc.*, **57**, 557 (1935)] modified procedure [C. A. Dornfeld, J. E. Callan, and G. H. Coleman, *Org. Syntheses*, **28**, 19 (1948)] followed by Solomon and Hennessy's[15] chromatographic technique was used to purify 90–95% phenanthrene (Gesellschaft f. Teerverwertung m. b. H. Duisburg-Meiderich, Germany).

(36) This was our average yield of *trans*-II diol for three runs. At variance with our results, R. F. Nystrom and W. G. Brown [*J. Am. Chem. Soc.*, **70**, 3738 (1948)] report a 98% yield of phenanthrenehydroquinone in a similar reduction.

(37) R. Wendland and J. La Fonde, *Org. Syntheses*, **34**, 76 (1954); L. F. Fieser and M. Fieser, *Organic Chemistry*, 3rd ed., D. C. Heath and Co., Boston, 1956, p. 757.

(38) R. F. Moore and W. A. Waters, *J. Chem. Soc.*, 3405 (1953).

(39) This is confirmation of the molecular compound nature of VI. The Rast camphor f.p. was 163°. At this temperature, VI must thermally dissociate into its component parts I (mol. wt., 208) and phenanthrenehydroquinone (mol. wt., 210). Each component will depress the f.p. independently of the other, and the f.p. depression is additive. However, since the f.p. depression is proportional to the molecular weight, the experimentally determined molecular weight (203) should be an average of the molecular weights of both components (209).

benzene to yield the red molecular compound VII, m.p. 156–157°, lit. m.p.: 156–157°[30,31a]; 158°.[8]

Anal. Calcd. for $C_{28}H_{18}O_3$: C, 83.56; H, 4.51; Mol. wt., 402. Found: C, 83.78; H, 4.71; Mol. wt., 202 (Rast camphor).[30,40]

A mixed m.p. of VI and VII was depressed to 130–145°. A benzene solution of VII was passed over aluminum oxide (Woelm, acid, activity grade 1). III fluoresces under ultraviolet light and the slow separation of VII into its components can be followed as III is eluted with large volumes of benzene. I remains adsorbed on the column.

(40) Rast camphor, f.p., 159°; Mol. wts. of I and II are 194 and 208, respectively; average, 201.

Acknowledgments. This research was supported in part by a grant from the Research Corporation and in part by a grant (C-3325) from the U. S. Public Health Service, National Cancer Institute. Grateful acknowledgment is hereby made to the donors of said funds.

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Oxidation of Phenols by Periodate[1]

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Polyhydric phenols and their monomethyl ethers have been oxidized by periodic acid. The extent of the reaction is determined by the orientation of the hydroxyl groups in the ring. Those with vicinal hydroxyls consume three moles of periodate very quickly and a fourth mole more slowly. The extent and rate of oxidation is very nearly the same for all compounds studied. The phenols with meta oriented hydroxyls react more slowly; the extent of the reaction depends upon the number of hydroxyl groups in the molecule. Hydroquinone quickly consumes one mole of oxidant; methylation of one of the hydroxyl groups increases the extent of the reaction.

While there are many reports in the literature concerning the use of periodic acid and its salts as reagents for degrading 1,2-glycols and related substances, very little work has been done on the action of these oxidants on phenols. In 1935, Clutterbuck and Reuter[2] reported the successful oxidation of a 1,2-diketone containing the resorcinol structure but restricted their attention to changes in the aliphatic portion of the molecule. In 1946, Pennington and Ritter[3] published the preliminary results of an investigation of the action of periodic acid on certain phenols of interest in lignin research as well as on lignin sulfonic acids. They reported that the appearance of yellow to red colorations accompanied the oxidation of all phenols studied except resorcinol and phloroglucinol. Windrath[4] has utilized such colorations in the development of a color and precipitation test for polyhydric phenols.

Quite recently, three different investigators have attacked this problem in much greater detail. Adler[5] and his coworkers have carefully studied the action of sodium periodate on guaiacol and many compounds representing lignin models. Initial studies on simple molecules showed that compounds containing the guaiacyl structure liberated about 0.9 mole of methanol in the oxidation, and this was shown to be very general for this type of structure if oxidation took place. In addition, *cis-cis*-muconic acid was identified among the oxidation products of catechol itself. They have not, as yet, reported any findings on either oxidation with periodic acid or oxidations of resorcinol and hydroquinone structures. Stumpf and Rumpf[6] have also examined the action of sodium periodate on guaiacyl-containing structures as well as on catechol and resorcinol. They report that all three dihydric phenols consume periodate quickly. Ishikawa and Nakajima[7] have studied the action of periodic acid on lignin; their studies have included some work on phenols.

Another type of periodate oxidation involves the oxidation of an active hydrogen on a carbon between two carbonyl groups; the resulting substance can then be cleaved as in a normal periodate oxidation. There are numerous examples of this.[8–10] Recently, Wolfrom and Bobbitt[11] have shown that 1,3-cyclopentanedione and 1,3-cyclohexanedione

(1) Presented before the Division of Organic Chemistry at the 132nd Meeting of the American Chemical Society, New York, September 1957.

(2) P. W. Clutterbuck and F. Reuter, *J. Chem. Soc.*, 1467 (1935).

(3) D. R. Pennington and D. E. Ritter, *J. Am. Chem. Soc.*, **68**, 1391 (1946); **69**, 187 (1947).

(4) O. M. Windrath, *Anal. Chem.*, **28**, 263 (1956).

(5) E. Adler and K. J. Bjorkvist, *Acta Chem. Scand.*, **5**, 241 (1951). E. Adler and S. Yllner, *Acta Chem. Scand.*, **7**, 570 (1953). E. Adler and S. Hernestam, *Acta Chem. Scand.*, **9**, 319 (1955).

(6) W. Stumpf and G. Rumpf, *Ana.*, **599**, 51 (1956).

(7) H. Ishikawa and T. Nakajima, *J. Japan Forest Soc.*, **36**, 106 (1954); **36**, 130 (1954). Trans. 62nd Meeting Japan Forest Soc., *J. Japan Forest Soc.*, Spec. Issue, 281 (1953). *Chem. Abstr.*, **50**, 3757h (1956).

(8) D. B. Sprinson and E. Chargaff, *J. Biol. Chem.*, **164**, 433 (1946).

(9) P. Fleury and J. Courtois, *Bull. soc. chim.*, [5] **14**, 358 (1947); [5] **15**, 190 (1948).

(10) C. F. Huebner, S. R. Ames, and E. C. Bubl, *J. Am. Chem. Soc.*, **68**, 1621 (1946).

(11) M. L. Wolfrom and J. M. Bobbitt, *J. Am. Chem. Soc.*, **78**, 2489 (1956).

TABLE I

PERIODIC ACID OXIDATION OF PHENOLS

Catechol (o-$C_6H_4(OH)_2$):								
Time (hr.)	2.5	21.5	45.5	69.5				
Moles HIO_4 consumed / Mole catechol	2.98	3.78	3.95	4.03				
Guaiacol (o-$CH_3OC_6H_4OH$):								
Time (hr.)	3.0	22.0	45.5	68.5				
Moles HIO_4 consumed / Mole guaiacol	3.21	3.90	4.04	4.16				
Pyrogallol (1,2,3-$C_6H_3(OH)_3$):								
Time (hr.)	0.5	5.0	23.5	54.5	126.5			
Moles HIO_4 consumed / Mole pyrogallol	3.01	3.39	3.75	4.03	4.15			
Resorcinol (m-$C_6H_4(OH)_2$):								
Time (hr.)	1.0	5.2	23.5	51.4	92.4	144	186	264
Moles HIO_4 consumed / Mole resorcinol	0.65	0.91	1.74	3.04	4.11	4.56	4.82	4.86
Resorcinol monomethyl ether (m-$CH_3OC_6H_4OH$):								
Time (hr.)	4.3	21.2	47	72	100	144	217	
Moles HIO_4 consumed / Mole of ether	0.48	1.03	1.58	2.15	2.64	3.38	3.84	
Phloroglucinol (1,3,5-$C_6H_3(OH)_3$):								
Time (hr.)	1.2	4.2	9.4	29.5	51.8	94.3	169.5	312
Moles HIO_4 consumed / Mole of phloroglucinol	2.18	3.03	4.14	5.78	6.13	6.50	6.60	6.87
Hydroquinone (p-$C_6H_4(OH)_2$):								
Time (hr.)	2.5	27.5	45.0					
Moles HIO_4 consumed / Mole of hydroquinone	1.13	1.14	1.22					
Hydroquinone monomethyl ether (p-$CH_3OC_6H_4OH$):								
Time (hr.)	4.5	24.0	48.0	71.5	149.5			
Moles HIO_4 consumed / Mole of ether	1.50	1.79	2.16	2.48	2.75			

consume periodate while noncyclic 1,3-diketones do not.

This paper reports the results of a study of the periodic acid oxidation of a number of phenols and their ethers. In most cases, deep colors developed which prevented a direct iodometric determination of the amount of periodate consumed. Even when the color was not pronounced fading end points were encountered when the reaction mixtures were titrated directly. Both these difficulties were overcome by use of the ion exchange procedure previously described.[12]

Results and Discussion. As has been reported by others[3,5,6] phenol and veratrole (1,2-dimethoxybenzene) were attacked only very slowly by periodic acid. For example, after periods of 2, 21, 45, and 69.5 hours, the amount of periodate consumed per mole of phenol was 0.18, 0.45, 0.72, and 0.92 mole respectively. After 65.5 hours, 0.45 mole of periodic acid per mole of veratrole was consumed. Data for the other compounds studied are summarized in Table I and plotted in Figures 1, 2, and 3.

The compounds listed in the first section of the table contain vicinal hydroxyl groups. These phenols all consumed about three moles of periodate rather quickly. The initial rapid consumption of three moles of oxidant was followed by a slower consumption of a fourth mole. The rate of oxidation was approximately the same for all three compounds as is indicated in Fig. 1. In all cases, the solutions eventually acquired a brownish color which rendered the solutions almost indistinguishable from one another.

The phenols with *meta* oriented hydroxyls studied are listed in the second section of the table. A quite different relationship exists among these phenols. Resorcinol slowly consumed somewhat more than four moles of oxidant. Its monomethyl ether was even more sluggish in its reaction. In the case of phloroglucinol, the reaction was more

(12) M. A. Smith and B. R. Willeford, Jr., *Anal. Chem.*, 26, 751 (1954).

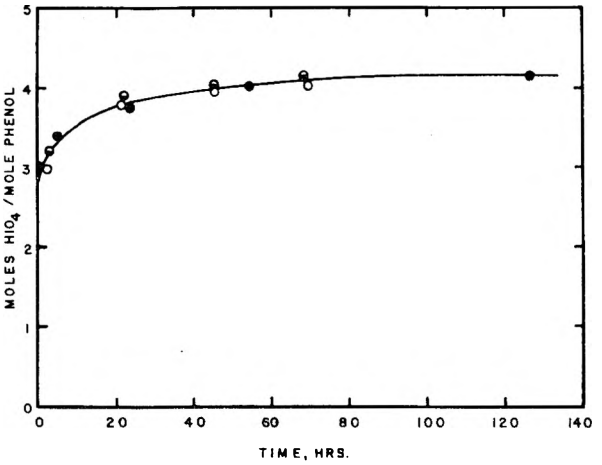


Fig. 1. Periodic acid oxidation of *ortho*-polyhydric phenols and derivatives. HIO_4 conc. = 0.01 M., *p*H = 2.1; open circles, catechol; half circles, guaiacol; closed circles, pyrogallol

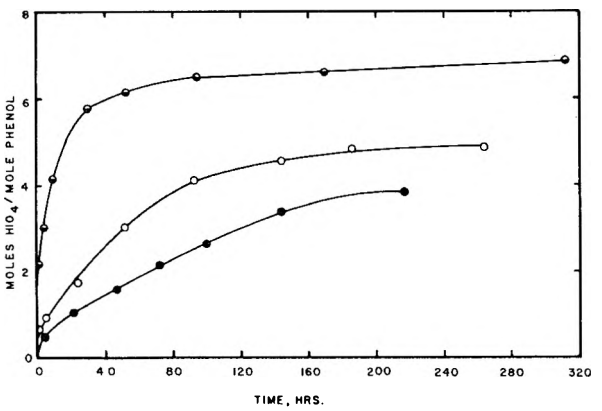


Fig. 2. Periodic acid oxidation of *meta*-polyhydric phenols and derivatives. HIO_4 conc. = 0.01 M., *p*H = 2.1; open circles, resorcinol; half circles, phloroglucinol; closed circles, resorcinol monomethyl ether

extensive and more rapid. About six moles of oxidant was quickly consumed, and this was followed by the slower consumption of a seventh mole. Fig. 2 summarizes these results.

The phenols with *para* oriented hydroxyl groups consumed less periodate than the members of the other two groups of polyhydric phenols. In the case of hydroquinone, only one mole of oxidant was consumed, and there was little further reaction. A light yellow color developed at once. Hydroquinone monomethyl ether was more reactive. It consumed over one mole of oxidant at once, and this was followed by a slower secondary reaction involving an additional one or two moles of periodate. These results are given in Fig. 3. The consumption of one mole of periodate by hydroquinone corresponds to the well known dehydrogenation of this compound.[13] Quinone was isolated in 89% yield from the reaction mixture.

(13) R. Criegee in *Newer Methods of Preparative Organic Chemistry*, Interscience Publishers, Inc., New York, 1948, p. 18.

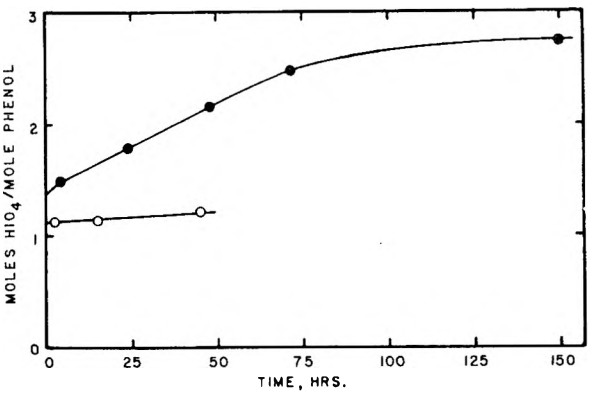
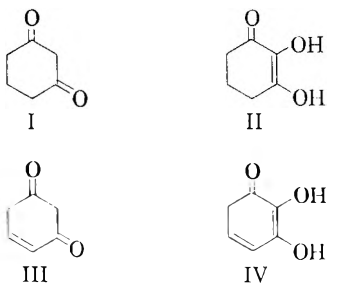


Fig. 3. Periodic acid oxidation of hydroquinone and its monomethyl ether. HIO_4 conc. = 0.01 M., *p*H = 2.1; open circles, hydroquinone; closed circles, hydroquinone monomethyl ether

That compounds such as phloroglucinol and resorcinol exhibit ketonic properties has been well established. Wolfrom and Bobbitt[11] found that 1,3-cyclohexandione(I) consumed four moles of periodate. One of their postulated intermediates is 2,3-dihydroxy-2-cyclohexenone(II); this was found to



consume three moles of periodate. The keto forms of resorcinol (III) and pyrogallol (IV) differ from these compounds only in the presence of a double bond in the ring, and it is possible that the initial consumption of four and three moles of periodate by resorcinol and pyrogallol respectively proceeds by a similar process. That both the rate and extent of oxidation is very nearly the same for pyrogallol and catechol is quite remarkable, and that methylation of one of the hydroxy groups (guaiacol) has little effect is particularly striking. Further work to elucidate the mechanism of these oxidations is currently being carried out.

EXPERIMENTAL

The experimental procedure was essentially the same as was reported previously.[12] Solutions of the phenol and periodic acid were prepared as described below for each compound studied. In all cases the *p*H of the solution was 2.1. At various intervals, 25 ml. aliquots (*ca.* 0.25 millimole of periodate) were withdrawn and passed through a 3 to 5 cm. bed of Amberlite IRA-400 ion exchange resin (acetate form) in an 8 mm. glass tube. A flow rate of 1 to 2 ml. per minute was used here and in the subsequent washing with 25 ml. of water. The column effluents were tested for iodate-periodate by the addition of an acidic potassium iodide–starch mixture. When the above procedure was followed, these tests were always negative. The periodate was then removed from the

column with 150 ml. of 5% potassium hydroxide solution. This effluent was neutralized with sulfuric acid, buffered with solid sodium hydrogen carbonate, cooled and analyzed for periodate by the usual arsenite-iodine procedure.[14]

Catechol. Commercial catechol was recrystallized from toluene. The reaction mixture was 9.94×10^{-3} molar in periodic acid and 1.80×10^{-3} molar in catechol (initial ratio of reactants 5.52/1). A moderate orange color developed immediately, and did not change noticeably after the first few minutes.

Guaiacol. Redistilled, center cut, b.p. 205°. Periodic acid $9.92 \times 10^{-3}M$, guaiacol $1.99 \times 10^{-3}M$, reactant ratio 4.98/1. When the reactants were mixed a yellow color developed quickly. However, in less than three minutes the solution was indistinguishable from the catechol–periodate mixture described above.

Pyrogallol. Commercial C. P. grade, m.p. 131–133°. Periodic acid $9.92 \times 10^{-3}M$, pyrogallol $1.98 \times 10^{-3}M$, reactant ratio 4.99/1. A deep brown color developed quickly when the reactants were mixed. In time the color became less pronounced and approached that of the two mixtures described above.

Resorcinol. Recrystallized from benzene, m.p. 110°. Periodic acid $9.97 \times 10^{-3}M$, resorcinol $1.26 \times 10^{-3}M$, reactant ratio 7.89/1. There was no color change on mixing the reactants.

Resorcinol monomethyl ether. Redistilled, center cut, b.p. 128–128.5°/13. Periodic acid $9.90 \times 10^{-3}M$, compound $1.85 \times 10^{-3}M$, reactant ratio 5.35/1. A light yellow color slowly developed when the reactants were mixed.

Phloroglucinol. Recrystallized from hot water and dried to constant weight *in vacuo* at 65°. This process yields anhydrous phloroglucinol. Periodic acid $9.97 \times 10^{-3}M$, phloroglucinol $8.72 \times 10^{-4}M$, reactant ratio 11.4/1. No color change observed on mixing.

Hydroquinone. Recrystallized from water, m.p. 161°. Periodic acid $9.94 \times 10^{-3}M$, hydroquinone $2.06 \times 10^{-3}M$, reactant ratio 4.83/1. A light yellow color quickly developed upon mixing.

Hydroquinone monomethyl ether, m.p. 54°. Periodic acid $9.90 \times 10^{-3}M$, compound $1.88 \times 10^{-3}M$, reactant ratio 5.26/1. The reaction mixture was yellow after 24 hr., slowly changed to brown, and finally became cloudy.

Phenol. Redistilled center cut, b.p. 181°. Periodic acid $9.80 \times 10^{-3}M$, phenol $3.06 \times 10^{-3}M$, reactant ratio 3.20/1. The solution turned light yellow on mixing the reactants and after 24 hr. became cloudy.

Veratrole. Redistilled center cut, b.p. 205°. Periodic acid $9.92 \times 10^{-3}M$, veratrole $1.89 \times 10^{-3}M$, reactant ratio 5.25/1. Light yellow solution produced on mixing the reactants.

Acknowledgment. We wish to express our appreciation to the Research Corporation and to the E. I. du Pont de Nemours Co. for grants to the Bucknell University Chemistry Department which made this work possible. Some of the preliminary experiments were carried out by Mr. Donald Dietz.

LEWISBURG, PA.

(14) E. L. Jackson, *Org. Reactions*, **2**, 341 (1944).

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Use of Nuclear Magnetic Resonance to Distinguish between Aliphatic Aldehyde and Ketone Derivatives

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Received August 4, 1958

The use of nuclear magnetic resonance to differentiate between aldehyde and ketone semicarbazones and 2,4-dinitrophenylhydrazones is described. The proton resonance of the N=C—H group of methylene chloride solutions of the dinitrophenylhydrazones occurs at −109 to −118 c.p.s. (at 40 Mc. relative to water as zero) and the corresponding resonance frequency of the semicarbazones is at −86 to −97 c.p.s. (40 Mc. relative to water) in the series of compounds studied. Other features of the NMR spectra are also discussed.

It has long been possible to distinguish aldehydes from ketones by standard chemical methods. In more recent years differences in physical properties, for example, differences in the carbonyl stretching frequency or the occurrence of the aldehydic C–H stretching band in infrared spectra, have been widely employed for the same purpose. However, in certain instances aldehydes and ketones, frequently liquids and obtained in low yield as degradation products, often from ozonolyses, can be isolated conveniently only as their derivatives. It is desirable, therefore, to have a method of determining whether such a derivative originated from an aldehyde or a ketone.

Ultraviolet[1–3] and infrared[2] spectral methods have been employed previously for this purpose. Thus, aldehyde 2,4-dinitrophenylhydrazones have been shown, in general, to have ultraviolet maxima at somewhat shorter wavelengths than those of similar derivatives of ketones,[1,2] while the color of the aldehyde derivatives deteriorated faster in basic solution than did that of the ketone derivatives.[2] In the infrared spectra of the dinitrophenylhydrazones of most compounds investigated the N–H stretching band was found at higher frequency in the ketone derivatives than in the aldehyde derivatives.[2] These correlations have proved useful; however, the shifts are slight and in marginal cases the ultraviolet and infrared spectral bands are

(1) G. D. Johnson, *J. Am. Chem. Soc.*, **75**, 2720 (1953).

(2) L. A. Jones, J. C. Holmes, and R. B. Seligman, *Anal. Chem.*, **28**, 191 (1956).

(3) A. E. Gillam and E. S. Stern, *An Introduction to Electronic Absorption Spectroscopy in Organic Chemistry*, 2nd ed., Edward Arnold, Ltd., London, 1958, p. 60.

TABLE I

NMR PEAKS OF 2,4-DINITROPHENYLHYDRAZONES

2,4-Dinitrophenylhydrazone[a] of	Peaks (c.p.s.)[b]							
	A	B				C	D	E
Acetaldehyde	−258	−174	−149	−139	−131	−118	−114	
		−171	−146	−137	−121	−113	+ 65	
Propionaldehyde	−250	−174	−148	−139	−131	−115	−113	
		−172	−146	−136	−121	−110	+ 67	
n-Butyraldehyde	−241	−168	−144	−135	−127	−113	−111	
		−165	−141	−133	−117	−108	+ 69	
Enanthaldehyde	−244	−172	−147	−140	−131	−114	−114	
		−169	−144	−138	−121	−109	+ 66	
Isobutyraldehyde	−249	−173	−149	−139	−130	−114	−113	
		−170	−147	−137	−120	−109	+ 69	
α-Ethylbutyraldehyde	−252	−172	−147	−139	−130	−110	−112	
		−171	−144	−136	−120	−104	+ 65	
Hydratropaldehyde	−244	−169	−144	−135	−127	−114	−107	−98
		−166	−141	−132	−117	−109	+ 71	
Acetone	−245	−173	−147	−137	−128		−112	
		−170	−144	−134	−118		+ 68	
Methyl ethyl ketone	−245	−169	−145	−136	−128		−110	
		−167	−142	−133	−119		+ 67	
Pinacolone	−244	−169	−145	−136	−128		−109	
		−167	−143	−132	−118		+ 68	
Cyclopentanone	−239	−171	−145	−137	−126		−113	
		−168	−142	−134	−116		+ 67	
4-Methylcyclohexanone	−248	−169	−144	−135	−128		−112	
		−166	−141	−132	−118		+ 65	
Benzylacetone	−245	−171	−146	−136	−126		−111	−99
		−169	−141	−134	−116		+ 70	
Methylene chloride							−112	
							+ 63	

[a] Methylene chloride solutions, concentrations found in Experimental section. [b] At 40 Mc., relative to water as zero. Peak interpretations are as follows: A, —NH—; B, 2,4-dinitrophenyl H's (*cf.* footnote 6 to text); C, —CH=N—; D, $^{13}CH_2Cl_2$ (solvent); E, phenyl H's.

difficult to assign with certainty to aldehyde or ketone starting materials.

An alternative method is one based on nuclear magnetic resonance spectroscopy, which may be expected *a priori* to offer advantage, since this method depends only on the presence or absence of the aldehyde hydrogen in the derivative. The present study was undertaken to determine the applicability and convenience of NMR spectroscopic methods in distinguishing between derivatives of aliphatic aldehydes and ketones. The hydrogen atom of the aldehyde functional group has been shown previously to give rise to resonance in the region −180 to −200 c.p.s. (relative to water as zero at 40 Mc.)[4a] while the substrate aldehyde proton resonance (—CH=N—) has been found at −88 and −62 c.p.s. for *syn* and *anti* forms of aldoximes (*cf.* below).[4b] It was hoped that the position of this hydrogen resonance would be equally distinctive in the semicarbazone and dinitrophenylhydrazone derivatives.

In the present investigation the NMR spectra of a number of aliphatic aldehyde and ketone 2,4-dinitrophenylhydrazones and semicarbazones have been determined in methylene chloride solution at 40 Mc.[5] Four of these spectra are presented in Fig. 1 and significant peaks of these four and other carbonyl derivatives are summarized in Tables I and II. In substantiation of expectation the NMR spectra of these derivatives conclusively distinguish between aldehyde and ketone substrate.

With the resolution available the aldehyde proton absorption appears as a doublet, due to H–H splitting (J_{HH} value 5–6 c.p.s.), in those dinitrophenylhydrazone and semicarbazone derivatives investigated (Tables I and II, Column C). For the dinitrophenylhydrazones the peaks are found in the region −104 to −118 c.p.s. and for the semicarbazones in the region −86 to −97 c.p.s. The appearance of these peaks readily distinguishes the

(4) (a) L. H. Meyer, A. Saika, and H. S. Gutowsky, *J. Am. Chem. Soc.*, 75, 4567 (1953); (b) W. D. Phillips, *Ann. N. Y. Acad. Sci.*, 70, 817 (1958).

(5) This study has been restricted to aliphatic compounds since the corresponding aromatic aldehyde and ketone derivatives were difficultly soluble in methylene chloride; similarly, the 2,4-dinitrophenylhydrazone and semicarbazone of formaldehyde were relatively insoluble. Spectra were determined, where possible, of 20% solutions of the derivatives, while lower concentrations gave less satisfactory spectra. However, no intrinsic limitation of utility to the aliphatic series is implied. The position of the substrate aldehyde hydrogen of conjugated unsaturated and aromatic aldehyde dinitrophenylhydrazones and semicarbazones might be expected to be in a position not far removed from that of the corresponding saturated aldehyde derivatives since position of the aldehyde hydrogen is essentially the same in saturated, unsaturated, and aromatic aldehydes.[4a]

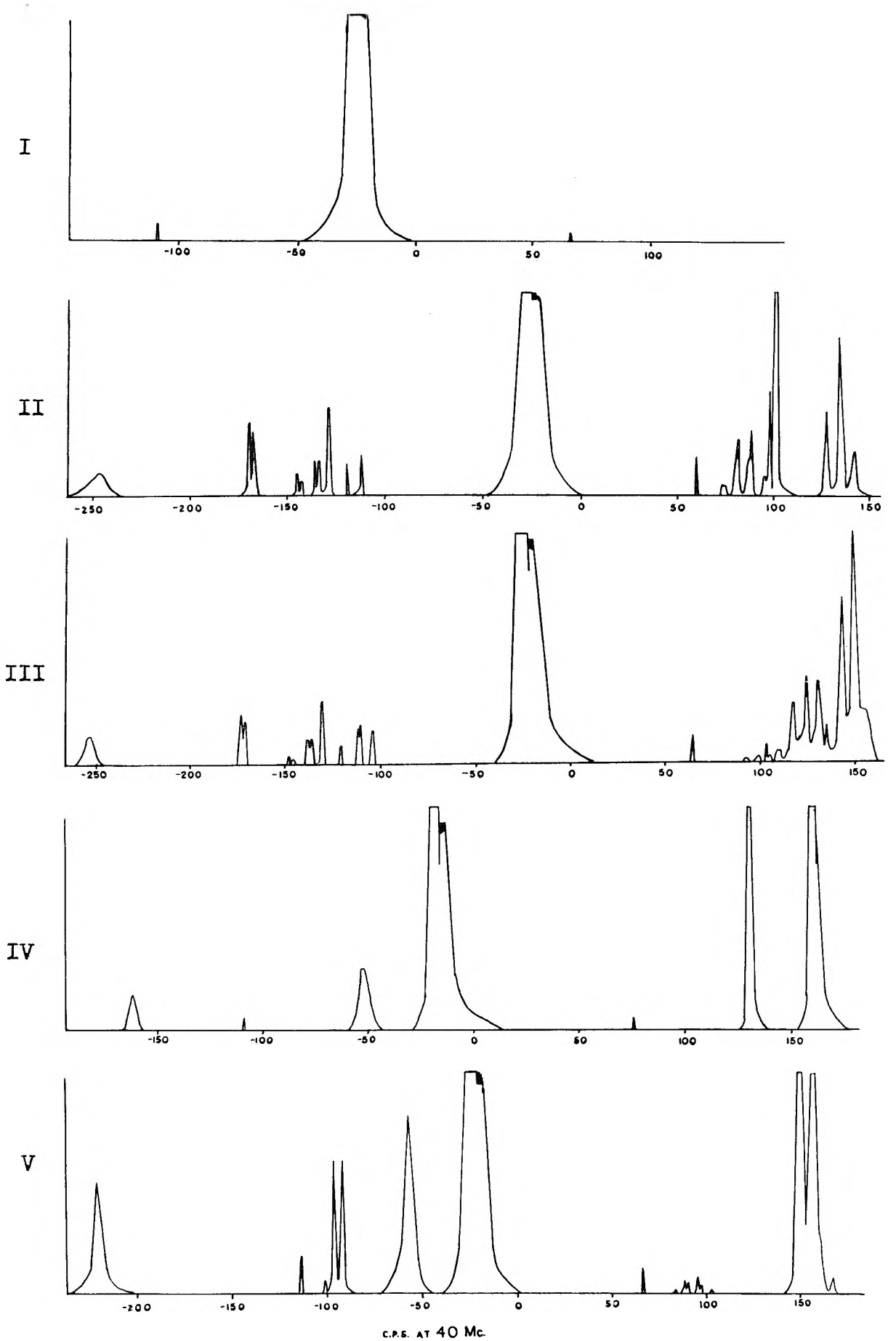

Fig. 1. NMR spectra of aldehyde and ketone derivatives. I. Methylene chloride solvent. II. Methyl ethyl ketone 2,4-dinitrophenylhydrazone. III. α-Ethylbutyraldehyde 2,4-dinitriphenylhydrazone. IV. Pinacolone semicarbazone. V. Isobutyraldehyde semicarbazone

TABLE II

NMR PEAKS OF SEMICARBAZONES

Semicarbazone[a] of	Peaks (c.p.s.)[b] A	B	C	D
Isobutyraldehyde	−209	−112 + 63	−97 −92	−57
α-Ethylbutyraldehyde	−210	−112 + 64	−92 −86	−58
Methyl *n*-amyl ketone	−164	−115 + 68		−48
Di-*n*-butyl ketone	−165	−113 + 67		−54
Pinacolone	−161	−114 + 65		−53

[a] Methylene chloride solutions, concentrations found in Experimental section. [b] At 40 Mc., relative to water. Peak interpretations are as follows: A, —NH—; B, $^{13}CH_2Cl_2$ (solvent); C, —CH=N—; D, NH_2.

spectra of the aldehyde derivatives from those of the corresponding ketone compounds (*cf.* Fig. 1). It is of interest that the —CH=N—proton absorption (multiplet) is found only in a single narrow region; hence, it may be assumed that the 2,4-dinitrophenylhydrazones and semicarbazones studied exist in a single isomeric form (*syn* or *anti*), in contrast to oximes, which were shown[4b] to exist in both *syn* and *anti* forms, of differing chemical shifts (at −88 and −62 c.p.s., respectively).

The semicarbazone spectra are somewhat simpler and more useful in distinguishing substrate types since they have no interfering aromatic protons absorbing in the same region (Table I, Column B) with the aldehyde proton, while the dinitrophenylhydrazones exhibit a total of eight peaks in the region at slightly lower field than that of the aldehyde substrate hydrogen.[6] The utility of the semicarbazone derivatives is limited, however, by their relatively low solubility in methylene chloride compared to the solubility of the 2,4-dinitrophenylhydrazones.

An additional peak in the same region as that of the aldehyde dinitrophenylhydrazone proton is due to the natural abundance (1%) of ^{13}C in the solvent methylene chloride.[7] This absorption occurs as a pair of satellite bands near −112 and +67 ($J_{^{13}CH}$ = 179 c.p.s.). Other readily assigned proton peaks at field values negative relative to that of water include broad —NH —proton absorption, in the regions −241 to −258 for dinitrophenylhydrazones, −210 for aldehyde semicarbazones, −163 for ketone semicarbazones, and broad —NH_2 proton absorption in the region −48 to −58 for the semicarbazones. The assignment of peaks is strengthened by the relative intensities of the bands. For example, in the spectrum of isobutyraldehyde semicarbazone (Fig. 1, Curve V) the —NH— peak at −209, the split —CH=N— peaks at −97 and −92, and the —NH_2 peak at −57 c.p.s. have relative intensities of 1:1:2, respectively.

Aromatic phenyl proton absorption was found at −99 c.p.s. in the spectra of dinitrophenylhydrazones of phenyl-substituted aldehydes and ketones. This band would be likely to overlap the absorption of the —CH=N— proton in semicarbazones; hence the maximal utility of semicarbazone spectra is restricted to aliphatic compounds. The —NH— and —NH_2 bands do not interfere with the assignment of the dinitrophenylhydrazones or semicarbazones as aldehyde or ketone derivatives, nor do the dinitrophenyl or methylene chloride satellite peaks described above when the spectrum of an unknown is compared to that of model compounds. Hence, the NMR spectra of these derivatives are definitive and useful criteria in assessing the nature of the substrate carbonyl compound.

EXPERIMENTAL[8]

2,4-Dinitrophenylhydrazones and semicarbazones were prepared by standard procedures;[9] melting points are reported in Tables III and IV.

NMR spectra of 2,4-dinitrophenylhydrazones and semicarbazones were calibrated in c.p.s. at 40 Mc. Samples were spun in a precision annular cell and an external sample of chloroform (−104 c.p.s.), benzene (−76 c.p.s.) or water (0 c.p.s.) was used for the calibration point in each spectrum. A Varian Associates Model V-4300-C high resolution *NMR* spectrometer with a 12-inch magnet and VK-3506 flux stabilizer was used to determine the spectra. Audio-frequency sidebands were generated with a Hewlett-Packard 200-CD audio-oscillator.

Methylene chloride was used as the solvent for both the 2,4-dinitrophenylhydrazones and the semicarbazones. The concentrations of the 2,4-dinitrophenylhydrazone solutions were 20% (weight/volume) with the following exceptions: acetaldehyde (9%), propionaldehyde (13%), enanthalde-

(6) Professor H. S. Gutowsky (personal communication) has interpreted the various dinitrophenyl peaks in terms of the following spin-spin splitting values: the C-3 proton, at a position *ortho* to both nitro groups, shows the greatest chemical shift but only small splitting (J_{HH} 2–3 c.p.s.) since it is split only by the proton *meta* to it (typical values, −171, −168), all splitting by *para* protons neglected; the C-6 proton, at a position *meta* to both nitro groups, shows the least chemical shift but larger splitting (J_{HH} 9–10 c.p.s.) since it is split by the proton *ortho* to it (typical values, −128, −118); the C-5 proton, at a position *ortho* to one nitro group and *para* to the other, shows an intermediate chemical shift with a small splitting constant (J_{HH} 2–3 c.p.s.) due to splitting by the proton *meta* to it, superimposed on a larger splitting constant (J_{HH} 9–10 c.p.s.) due to splitting by the adjacent *ortho* proton (typical values, −147, −144, −137, −134). We are indebted to Professor Gutowsky for this interpretation [*cf.* also H. S. Gutowsky, C. H. Holm, A. Saika, and G. A. Williams, *J. Am. Chem. Soc.*, 79, 4596 (1957)].

(7) (a) A. D. Cohen, N. Sheppard, and J. J. Turner, *Proc. Chem. Soc.*, 118 (1958); (b) H. S. Gutowsky, unpublished results.

(8) All melting points are corrected. The NMR spectra were obtained by Mr. B. A. Shoulders. The reproductions in Fig. 1 are tracings of the original spectra with the base lines adjusted to coincide with the bottoms of the tracings.

(9) 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, pp. 218–19.

TABLE III

MELTING POINTS OF 2,4-DINITROPHENYLHYDRAZONES

2,4-Dinitrophenyl-hydrazone of	M.P., °C. Found	M.P., °C. Reported	Reference
Acetaldehyde	148–148.5	147 (162)	10
Propionaldehyde	147–148	154	10
n-Butyraldehyde	122–123	122	10
Enanthaldehyde	106.0–106.5	106	10
Isobutyraldehyde	182–183	182	10
α-Ethylbutyraldehyde	94–95	94	11
Hydratropaldehyde	136–137	136–137	12
Acetone	126–127	126	13
Methyl ethyl ketone	118–119	115	10
Pinacolone	126–127	125	16
Cyclopentanone	146–146.5	146–147	13
4-Methylcyclohexanone	133.5–134.0	134.7–135.1	15
Benzylacetone	127–128	125–126.3	14

TABLE IV

MELTING POINTS OF SEMICARBAZONES

Semicarbazone of	M.P., °C. Found	M.P., °C. Reported	Reference
Isobutyraldehyde	118–119	125	17
α-Ethylbutyraldehyde	95–96	96	17
Methyl *n*-amyl ketone	123–124	121–123	18
Di-*n*-butyl ketone	90–91	90	19
Pinacolone	157–158	157	20

hyde (7%). The concentrations of the semicarbazone solutions were as follows: isobutyraldehyde 20%, α-ethylbutyraldehyde 15%, methyl *n*-amyl ketone 7%, di-*n*-butyl ketone 14%, pinacolone 10%.

URBANA, ILL.

(10) O. L. Brady and G. V. Elsmie, *Analyst*, **51**, 77 (1926).
(11) H. Brunner and E. H. Farmer, *J. Chem. Soc.*, 1039 (1937).
(12) F. Ramirez and A. F. Kirby, *J. Am. Chem. Soc.*, **75**, 6026 (1953).
(13) N. R. Campbell, *Analyst*, **61**, 391 (1936).
(14) J. F. Bunnett, J. L. Marks, and H. Moe, *J. Am. Chem. Soc.*, **75**, 985 (1953).
(15) H. Adkins and A. G. Rossou, *J. Am. Chem. Soc.*, **71**, 3836 (1949).
(16) C. F. H. Allen, *J. Am. Chem. Soc.*, **52**, 2955 (1930).
(17) Ref. (9), p. 283.
(18) W. S. Rapson and R. G. Shuttleworth, *J. Chem. Soc.*, 99 (1940).
(19) Ref. (9), p. 316.
(20) A. Michael, *J. Am. Chem. Soc.*, **41**, 417 (1919).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CANISIUS COLLEGE]

Abnormal Beckmann Rearrangements in Polyphosphoric Acid. I. Benzil Monoxime and Related Oximes[1,2]

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Received August 15, 1958

The Beckmann rearrangement of alpha-benzil monoxime and alpha-benzoin oxime in polyphosphoric acid to yield benzonitrile as one of the rearrangement products in each case is reported. These data, together with the direct nitrosation of desoxybenzoin, indicate the rearrangements of these oximes in polyphosphoric acid are examples of the abnormal Beckmann rearrangement rather than the normal Beckmann rearrangement as previously reported. The rearrangement of alpha-benzil dioxime in polyphosphoric acid quantitatively yields 3,5-diphenyl-1,2,4-oxadiazole.

The Beckmann rearrangement of alpha-benzil monoxime and alpha-benzoin oxime has been the subject of extensive study.[4] Although the nature of the products has varied with the acid catalyst used and the conditions of the reaction, in general, each oxime has been shown to yield products which could arise from an initial normal Beckmann rearrangement.[5] It has been reported,[6] that alpha-benzil monoxime (I) in polyphosphoric acid at 120° undergoes the Beckmann transformation to yield initially dibenzamide (II) as shown in Fig. 1. The dibenzamide was believed to be hydrolyzed by the medium to yield the isolated products, namely, benzoic acid and benzamide. These

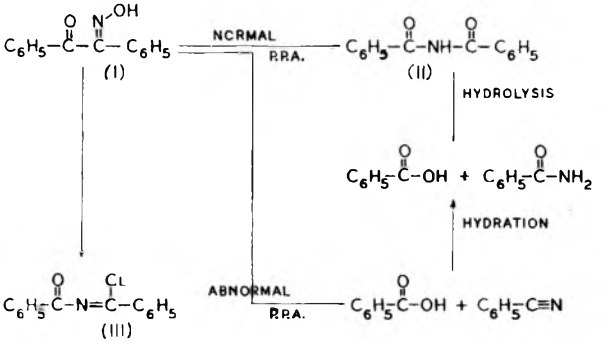

Figure 1

(1) Preliminary results of this investigation are reported in *Tetrahedron*, **3**, 90 (1958).
(2) This work was supported by a Frederick Gardner Cottrell grant from the Research Corp.
(3) Abstracted in part from the thesis submitted by F. A Mikulski to the Department of Chemistry, Canisius College in fulfillment of the requirements for the Bachelor of Science degree.
(4) A. H. Blatt, *Chem. Revs.*, **12**, 215 (1933).
(5) N. V. Sidgwick, *The Organic Chemistry of Nitrogen*, (revised and rewritten by T. W. J. Taylor and W. Baker), Oxford University Press, 1942, p. 182.
(6) E. C. Horning, V. L. Stromberg, and H. A. Lloyd, *J. Am. Chem. Soc.*, **74**, 5153 (1952).

data were in general agreement with the rearrangement of alpha-diketone monoximes on treatment with other acid catalysts. For example, treatment of alpha-benzil monoxime with phosphorus pentachloride in ether yields *N*-benzoylbenzimido chloride (III) which on hydrolysis yields ammonia and two molecular equivalents of benzoic acid. Recently, it has been reported[7] that certain α,α-disubstituted ketoximes rearranges abnormally in polyphosphoric acid. Presumably, these rearrangements proceed through a nitrile intermediate. Also, the behavior of amides in polyphosphoric acid solution[8] indicates that hydrolysis of the postulated dibenzamide intermediate would not have occurred under the conditions of the Beckmann rearrangement. Finally, it has been shown that benzonitrile can be hydrolyzed to benzamide almost quantitatively in polyphosphoric acid at temperatures similar to those used to effect the Beckmann rearrangement.[9] These data indicated that the rearrangement of alpha-benzil monoxime in polyphosphoric acid may proceed *via* the abnormal path as has been observed in the base catalyzed rearrangement of this substance.[10] For example, alpha-benzil monoxime on treatment with benzene–sulfonyl chloride in pyridine or alkali solution undergoes cleavage to yield benzonitrile and benzoic acid. This direct cleavage reaction has been called a second-order Beckmann rearrangement or an abnormal Beckmann rearrangement.

In light of these studies, it was of interest to reinvestigate the Beckmann rearrangement of alpha-benzil monoxime in polyphosphoric acid. However, it was desirable to carry out this investigation under experimental conditions such that the hydrolysis of the nitrile, if produced, would be minimized. It was also of interest to extend the study to include the rearrangement of alpha-benzoin oxime and alpha-benzil dioxime in this medium.

The rearrangement of alpha-benzil monoxime was carried out at three temperatures. These reactions are summarized in Table I. The rearrangement of alpha-benzil monoxime, therefore, initially yields benzonitrile which at higher temperatures is hydrolyzed by the medium to benzamide. This was confirmed by heating alpha-benzil monoxime with polyphosphoric acid for 8 hr. The reaction mixture was then divided into two parts; the first part was hydrolyzed with ice water and the products separated in the usual manner to yield predominantly benzoic acid and benzonitrile, the second part was heated at 120° for 15 min. and the reaction mixtures treated in an identical fashion. The products were benzoic acid and benzamide only. No nitrile could be detected.

TABLE I

VARIATION OF THE PRODUCTS OF THE REARRANGEMENT OF ALPHA-BENZIL MONOXIME WITH TEMPERATURE

Temp., °C.	Time, Min.	Yield, %	Product
25	420	96	Benzoic acid
		87	Benzonitrile
		3	Benzamide
65	90	98	Benzoic acid
		80	Benzonitrile
		15	Benzamide
120[a]	15	98	Benzoic acid
		92	Benzamide
		0	Benzonitrile

[a] Ref. 6; report the product distribution under slightly different conditions (temp. 90–115°.C) to be: benzoic acid, 100%; benzamide, 40%; benzonitrile, none detected.

Further substantiation of these results was obtained by the direct nitrosation of desoxybenzoin[11] in polyphosphoric acid at 25°. As expected, the nitroso compound, so produced, rearranged under the acid conditions to the oxime which further rearranged, *in situ*, to yield benzonitrile and benzoic acid. None of the postulated reaction intermediate, dibenzamide, was observed under any of the reaction conditions used in this study.

The rearrangement of alpha-benzoin monoxime was carried out under the same time-temperature conditions as were used for alpha-benzil monoxime (Table I). In all cases, an appreciable amount of tarring of the reaction mixture took place. However, at 25°, benzaldehyde was isolated in 33% yield and benzonitrile in 26% yield by column chromatography over activated alumina, which separated the benzonitrile-benzaldehyde fraction from the tars, followed by micro fractional distillation. At 120°, a small amount of benzaldehyde was isolated (as the 2,4-dinitrophenylhydrazone derivative) and a small amount of a yellow solid, identified *via* its infrared spectrum as benzamide, was also obtained. Further attempts to separate and identify components of the reaction mixture were not undertaken. It is clear, however, that the nitrile is produced in appreciable amounts and that the rearrangement most probably follows the "abnormal" path in polyphosphoric acid.

The rearrangement of alpha-benzil dioxime (IV) in polyphosphoric acid at 25° yields predominantly 3,5-diphenyl-1,2,4-oxadiazole (V). However, frac-

(7) R. K. Hill and R. T. Conley, *Chem. & Ind. (London)*, 1314 (1956).

(8) (a) R. T. Conley, doctoral dissertation, Princeton University (1957); (b) R. K. Hill, *J. Org. Chem.*, **22**, 830 (1957); (c) C. T. Elston, doctoral dissertation, University of Illinois (1954).

(9) H. R. Snyder and C. T. Elston, *J. Am. Chem. Soc.*, **76**, 3039 (1954).

(10) (a) A. Werner and A. Piquet, *Ber.*, **37**, 4295 (1904); (b) O. Diels and M. Stern, *Ber.*, **40**, 1629 (1907).

(11) It has come to our attention since the submission of the preliminary results of this investigation, Ref. 1, that a similar experiment was performed by C. T. Elston, Ref. 8c. At that time this author concluded the Beckman rearrangement of alpha-benzil monoxime did not proceed normally as reported by Horning, Stromberg, and Lloyd, Ref. 6 [See F. D. Popp and W. E. McEwen, *Chem. Revs.*, **58**, 372 (1958).]

tional crystallization of the crude product from absolute alcohol yielded *N*-phenyl-*N*-benzoylurea (VI) (4%). At 120°, only 3,5-diphenyl-1,2,4-oxadiazole could be isolated (99%). These data are summarized in Fig. 2. The rearrangement in this

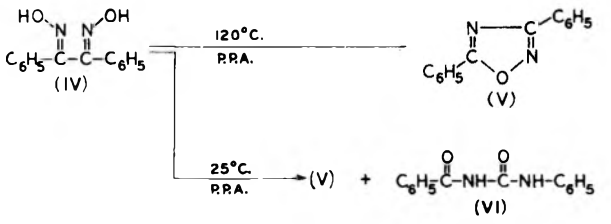

Figure 2

case undoubtedly follows the normal Beckmann path. Rearrangement occurs at one oximino-group followed by cyclization to form the oxadiazole ring. At the lower temperature, however, a small amount of a doubly rearranged product was obtained. This product could not have arisen from the alpha-dioxime.[4] Therefore, it must be assumed that a small amount of inversion of configuration must have occurred during the rearrangement since the product would be expected to be formed only from the gamma-dioxime on the basis of a trans migration of the phenyl groups.

From the results of this study, it is quite clear that the monoximes of both benzil and benzoin follow the abnormal Beckmann rearrangement path in polyphosphoric acid rather than the normal rearrangement previously postulated by Horning, Stromberg, and Lloyd.[6] Further studies of the rearrangement of alpha-diketoximes in polyphosphoric acid are presently being carried out and will be reported at a later time.

Examples of typical rearrangement procedures are given in the Experimental section. The rearrangement products were identified in all cases with authentic samples prepared by reported procedures. The criteria of identity were two; no depression in mixed melting point and identical infrared spectra.

EXPERIMENTAL

All melting points were determined on a Thomas-Hoover capillary melting point apparatus and are corrected. The infrared spectra used for comparison were determined using a Baird, model 2-B, double beam, recording spectrophotometer. The reactants were obtained from commercial sources and purified by repeated crystallization.

Rearrangement of alpha-benzil monoxime. A mixture of 10 g. (0.045 mole) of alpha-benzil monoxime and 120 g. of polyphosphoric acid was stirred intermittently in a 250-ml. Erlenmeyer flask for 8 hr. at 25°C. The mixture was hydrolyzed over crushed ice and water. The hydrolysis mixture was extracted 6 times with 150-ml. portions of ether. The combined ether extracts were washed 3 times with 50-ml. portions of 10% sodium hydroxide solution. Acidification of the basic wash solution with dilute hydrochloric acid in the cold yielded 5.28 g. (96%) of benzoic acid, m.p. 121.5–122°. A mixed melting point with an authentic sample showed no depression, m.p. 121.5–122°.

The combined ether extracts were dried over magnesium sulfate, filtered, and evaporated. The products, obtained as a light yellow oil, were chromatographed over a small column of activated alumina in petroleum ether (65–70° fraction). Elution of the column with 1:1 petroleum ether–diethyl ether mixture yielded on evaporation of the solvents 3.94 g. (87%) of benzonitrile, characterized by its infrared spectrum, conversion to benzoic acid and ammonia with hot 25% potassium hydroxide solution, and hydration to benzamide, m.p. 128–130° with polyphosphoric acid, according to the method described by Snyder and Elston.[9] Elution of the column with 1:1 chloroform–diethyl ether yielded on evaporation of the solvents 0.16 g. (3%) of benzamide, m.p. 128–130°. Mixed melting point with an authentic sample showed no depression, m.p. 128.5–130°. Further elution of the column with first chloroform and then ethyl alcohol did not remove further material from the column.

Nitrosation of desoxybenzoin in polyphosphoric acid. A mixture of 9.80 g. (0.05 mole) of desoxybenzoin, 3.45 g. zoin, 3.45 g. (0.05 mole) of sodium nitrite, and 125 g. of polyphosphoric acid was stirred at 25° for 7.5 hr. The mixture was hydrolyzed over crushed ice and water. A thick, brown paste separated. The aqueous mixture was extracted 5 times with 100-ml. portions of ether.

The combined ether extracts were washed 3 times with 50-ml. portions of 10% sodium hydroxide solution. On acidification of the combined base washings, 4.60 g. (75%) of benzoic acid was obtained m.p 118.5–121°. The ether extracts were dried over anhydrous magnesium sulfate, filtered, and evaporated. The residue was distilled *in vacuo* to yield 3.40 g. (67%) of benzonitrile, b.p. 68–70°/10 mm. and 2.4 g. of residue which on cooling solidified. The low melting, solid residue was taken up in a minimum amount of chloroform and passed thru a small alumina column to yield on evaporation of the chloroform solution 2.1 g. (21.4%) of desoxybenzoin, m.p. 55–56°. No depression of the mixed melting point with the starting material was observed, m.p. 55–56.5° and the infrared spectra of the two were identical.

Rearrangement of alpha-benzoin oxime. A mixture of 5.0 g. (0.022 mole) of alpha-benzoin oxime and 90 g. of polyphosphoric acid was stirred intermittently for 8 hr. at 25°. The black reaction mixture was hydrolyzed in the usual fashion. A black, viscous mass separated. The aqueous mixture was thoroughly extracted with ether. The ether extracts were combined, dried over anhydrous magnesium sulfate, filtered, and evaporated. The residue was taken up in a minimum amount of chloroform and chromatographed over an activated alumina column packed in ether. The column was eluted with 1:1 chloroform ether. On evaporation, of the first 150 ml. of eluent, a light yellow benzaldehyde-benzonitrile mixture was obtained. This mixture was distilled *in vacuo* to yield 0.76 g. (33%) of benzaldehyde, b.p. 60–63°/10 mm., characterized by its 2,4 dinitrophenylhydrazone derivative, m.p. 236–237.5° and its semicarbazone derivative, m.p. 222.5° (neither derivative showed depression on mixed melting point determination with derivatives prepared from an authentic sample of benzaldehyde) and 0.58 g. (26%) of benzonitrile. No separation of the tarry residue remaining on the column could be effected by elution with successively more polar solvent mixtures.

Rearrangement of alpha-benzil dioxime. A mixture of 5.2 g. (0.021 mole) of alpha-benzil dioxime and 80 g. of polyphosphoric acid were heated together at 120° for 12 min. The reaction mixture was hydrolyzed in the usual manner. A flocculent white precipitate formed immediately. After filtration and vacuum drying 4.62 g. (99%) of 3,5- diphenyl-1,2,4-oxadiazole was obtained, m.p. 108–108.5°. Repeated recrystallization from absolute ethanol or sublimation did not alter the melting point.

Anal. Calcd. for $C_{14}H_{10}N_2O$: C, 52.65; H, 8.82; N, 24.52. Found: C, 52.60; H, 8.76; N, 24.23.

Mixed melting point with an authentic sample prepared

by the method outlined by Beckmann[12] showed no depression, m.p. 108–108.5°.

Acknowledgments: The authors wish to thank Professor R. K. Hill of Princeton University for his many comments and suggestions in connection with these investigations and Canisius College for a Faculty Research Grant to R.T.C. to aid in the preparation of this communication.

(12) E. Beckmann, *Ber.*, 22, 1589 (1889).

BUFFALO 8, N. Y.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CINCINNATI]

Substituted γ-Lactones. II. Some Electrophilic Substitution Reactions of α-Benzylidene-γ-butyrolactone

HANS ZIMMER AND JOHANNES ROTHE[1]

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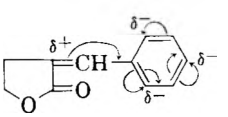
In electrophilic substitution reactions, α-benzylidene-γ-butyrolactone (I) is similar to cinnamic acid. It can be nitrated predominantly in the para position. With chlorosulfonic acid it gives the *p*-chlorosulfonyl derivative (VIII). The structures of the substitution products have been verified by oxidative degradation. The reduction of the three isomeric α-nitrobenzylidene-γ-butyrolactones and the preparation of several derivatives of the α-aminobenzylidene-γ-butyrolactones obtained is described.

In a previous paper[2] the condensation of several aldehydes with butyrolactone was described. It has been found that this reaction did not proceed well with nitrobenzaldehydes or with *p*-acetamidobenzaldehyde, which compounds gave small yields or substantially no yields at all. However, nitro- and amino-substituted α-benzylidene- γ-butyrolactones and some of their derivatives were desired in order to investigate their pharmacological properties; therefore, a nitration of the readily available[3] α-benzylidene-γ-butyrolactone (I) was attempted. The nitration products obtainable from this reaction could serve as intermediates in the preparation of the corresponding amino compounds and derivatives thereof. We also were interested in sulfonic acid derivatives of I and hence ran a sulfochlorination of I.

Reaction of I with potassium nitrate in concentrated sulfuric acid at low temperature[4] furnished a 60% yield of α-(*p*-nitrobenzylidene)-γ-butyrolacrone (II) and a lesser amount of the *o*-isomer (III). The structures of the compounds obtained were proven by oxidative degradation to the corresponding nitrobenzoic acids, and, in the case of II, by comparison with an authentic sample, obtained by a condensation between *p*-nitrobenzaldehyde and butyrolactone.[2] In one experiment which was carried out with an excess of potassium nitrate, a small yield of a dinitro product, presumably α-(2,4-dinitrobenzylidene)-γ-butyrolactone (IV), was obtained.

These experiments show that in I electrophilic substitution occurs in the *p*- and *o*-positions. This can be explained by assuming that during the attack of the nitrating agent a time-variable electromeric electron shift occurs similarly to that observed in the nitration of cinnamic acid,[5] thus, activating the ortho and para positions towards an electrophilic attack: The ratio of the yields of II



and III is about 3.3:1. Underwood and Kochmann,[5b] in the nitration of cinnamic acid, observed a para: ortho ratio of about 2.5:1. The greater tendency of I towards para-substitution can be explained by the appreciable amount of steric hindrance imposed by the lactone ring on the ortho positions. Accordingly the sulfochlorination of I gave predominantly the *p*-chlorosulfonyl derivative (VIII). The corresponding ortho derivative could not be isolated. Probably due to increased steric hindrance, its formation might occur only to a minor extent, if any.

Reduction of II, III, and of α-(*m*-nitrobenzylidene)-γ-butyrolactone (V)[2] with stannous chloride and concentrated hydrochloric aicd gave solid complexes which on treatment with aqueous ammonia and subsequent extraction with an organic solvent such as chloroform or tetrahydrofuran gave the corresponding amino derivatives in high

(1) Chattanooga Medicine Company Post-doctorate Research Fellow 1956–1958. Recipient of a Fulbright Travel Grant. Present address: Department of Chemistry, Harvard University, Cambridge, Mass.

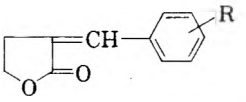
(2) H. Zimmer and J. Rothe, *J. Org. Chem.*, 24, 28 (1959).

(3) W. Reppe and co-workers, *Ann.*, 596, 158 (1955).

(4) *e.g.*, W. Borsche, K. Diacont, and H. Hanau, *Ber.*, 67, 675 (1934); T. Kariyone and T. Fukui, *J. Pharm. Soc. Japan*, 68, 276 (1948); *Chem. Abstr.*, 45, 9520i (1951).

(5) (a) E. E. Royals, *Advanced Organic Chemistry*, Prentice-Hall, Inc., Englewood Cliffs, N. J., 1954, p. 439. (b) H. W. Underwood Jr. and E. L. Kochmann, *J. Am. Chem. Soc.*, 48, 254 (1926).

TABLE I



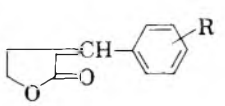
SUBSTITUTED α-BENZYLIDENE-γ-BUTYROLACTONES

R	Formula	M.P., °C.	[a]	Carbon, %		Hydrogen, %		Nitrogen, %	
				Calcd.	Found	Calcd.	Found	Calcd.	Found
m-Acetamido-	$C_{13}H_{13}NO_3$	181.5–182	M					6.06	6.21
p-Acetamido	$C_{13}H_{13}NO_3$	200–201[b]	M						
m-Benzenesulfonamido	$C_{17}H_{15}NO_4S$	157–158	M	61.99	62.10	4.59	4.73		
p-Benzenesulfonamido	$C_{17}H_{15}NO_4S$	226–228d.	E	61.99	61.76	4.59	5.14	4.25	3.90
m-(*p*-Nitrobenzenesulfonamido)	$C_{17}H_{14}N_2O_6S.H_2O$	238–239d.	M	52.03	51.87	4.11	4.58		
p-(*p*-Nitrobenzenesulfonamido)	$C_{17}H_{14}N_2O_6S.H_2O$[c]	212–214d.	M	52.03	51.53	4.11	4.48		
m-(*p*-Acetamidobenzenesulfonamido)	$C_{19}H_{18}N_2O_5S.H_2O$	251–252.5d.	W[d]	56.42	56.07	4.95	5.19		
p-(*p*-Acetamidobenzenesulfonamido)	$C_{19}H_{18}N_2O_5S.H_2O$	253–253.5d.	X	56.42	56.71	4.95	4.90		

[a] Solvent for recrystallization: M = methanol, E = ethanol, W = water, X = purified by extracting with dioxane-ethanol. [b] Mixed m.p. with an authentic[2] sample: 200–201°. [c] Found after drying at 50° (high vacuum): C, 54.32; H, 4.21. Calcd. for $C_{17}H_{14}N_2O_6S$: C, 54.54; H, 3.77. [d] Analytical sample from dimethylformamide-ether.

yields. The *m*-(VI) and *p*-compounds (VII) could be hydrogenated[2] to the corresponding α-aminobenzylbutyrolactones. α-(*o*-Aminobenzylidene)-γ-butyrolactone appears to be somewhat unstable in solution, and its hydrogenation does not seem to follow the normal path. Further work on this compound is in progress.

Some acyl and sulfonyl derivatives of VI and VII were also prepared (see Table I). VIII on standing with concentrated ammonia gave the sulfonamide IX. IX was oxidized to *p*-sulfonamidobenzoic acid thus verifying the structure of VIII. Treatment of VIII with hydrazine and aniline, respectively, gave the expected derivatives. Some



I. R = H
II. R = *p*-NO_2
III. R = *o*-NO_2
IV. R = x.y-$(NO_2)_2$
V. R = *m*-NO_2
VI. R = *m*-NH_2
VII. R = *p*-NH_2
VIII. R = *p*-SO_2Cl
IX. R = *p*-SO_2NH_2

of the compounds showed interesting pharmacological properties. The results will be published elsewhere.

EXPERIMENTAL

Melting points are uncorrected. Microanalyses by A. Bernhardt, Mikroanalytisches Laboratorium im Max-Planck-Institut, Mülheim/Ruhr, Germany.

Nitration of α-benzylidene-γ-butyrolactone (I). A solution of 52.2 g. (0.3 mole) of I in 180 cc. of conc. sulfuric acid was cooled by means of an ice-salt bath. While being stirred, a solution of 33 g. (0.33 mole) of potassium nitrate in 140 cc. of conc. sulfuric acid was added dropwise within 1 hr.; the internal temperature during the addition was held between 0 and +5°. The mixture was kept for 3 more hours in the ice-bath, then poured on ice. A slightly yellow precipitate occurred which was filtered by suction, thoroughly washed with water until the washings were neutral, then washed with cold methanol. This crude product was treated briefly with 250 cc. of hot methanol and filtered hot; *α-p-nitrobenzylidene)-γ-butyrolactone (II)* which remained undissolved was washed with hot and cold methanol, then with ether. The product was sufficiently pure for reduction, yield 40.0 g. (61%), m.p. 201–202°.

An analytical sample, after 3 recrystallizations from tetrahydrofuran, had the same m.p.; yellowish needles.

Anal. Calcd. for $C_{11}H_9NO_4$: C, 60.27; H, 4.14. Found: C, 60.02; H, 3.92.

A mixed m.p. with an authentical sample (m.p. 202–203°) obtained by condensation of *p*-nitrobenzaldehyde with butyrolactone[2] was 201–203°. II is rather insoluble in cold common solvents except in acetic acid. It is soluble in warm dioxane, acetone, and ethyl acetate.

The methanolic filtrates of I precipitated on concentration the isomeric *α-(o-nitrobenzylidene)-γ-butyrolactone (III)*; after one recrystallization from methanol, 11.9 g. (18%), m.p. 96–97°, were obtained. After two more recrystallizations from methanol, the m.p. of the yellowish leaflets was 96–97.5°.

Anal. Calcd. for $C_{11}H_9NO_4$: C, 60.27; H, 4.14; N, 6.39. Found: C, 60.15; H, 4.03; N, 6.58.

Formation of α-(x,y-dinitrobenzylidene)-γ-butyrolactone (IV). A solution of 17.4 g. (0.1 mole) of I in 60 cc. of sulfuric acid was prepared. With external cooling (ice) and stirring, a solution of 22 g. (0.22 mole) of potassium nitrate in 100 cc. of sulfuric acid was added gradually within 15 min. during which the internal temperature was kept at 22–25°. Stirring was continued for 2 more hours at 20–30°, then the mixture was poured on ice. A resinous precipitate occurred which was filtered, washed, and recrystallized from 50 cc. of methanol and 3.9 g. (15%) of crude material, m.p. *ca.* 131–136° (not clear until 180°), were obtained.

Not less than 250 cc. of methanol were required for the recrystallization of the crude product; on cooling, two different kinds of crystals appeared which were filtered and separated manually: octahedra (m.p. 131.5–132.5°, 2.8 g.) and fine needles (m.p. 185–190°, 0.3 g., probably II).

The octahedra were again recrystallized from 100 cc, of methanol yielding yellowish cubes, m.p. 134–137°, and a small amount of a brownish powder, m.p. 159–190°. The cubes were separated manually and recrystallized 3 more times from methanol to give the pure *α-(x,y-dinitrobenzylidene)-γ-butyrolactone* (*IV*) m.p. 136.5–137.5°.

Anal. Calcd. for $C_{11}H_8N_2O_6$: C, 50.01; H, 3.05; N, 10.60. Found: C, 50.07; H, 3.04; N, 10.72.

Various crystalline fractions were obtained from the aqueous and the first methanolic filtrates, indicating that some II and III had been formed during the reaction. Because of the abundant resinous by-products, however, they were not investigated further.

Verification of the structures of II and III. Boiling of II for 10 hr. with an excess of potassium permanganate in sodium carbonate solution, removal of manganese dioxide, and acidification gave *p*-nitrobenzoic acid (m.p. 239–243°; mixed m.p. with an authentic sample: 239–242°).

Similarly, a small amount of *o*-nitrobenzoic acid (m.p. 138–140°) was obtained from III. Mixed m.p. with an authentic sample (m.p. 145.5–148°): 142–144°.

Oxidation of IV with permanganate led to an acid (m.p. 145–150° dec.) the amount of which was too small for further purification. Mixed m.p. with an authentic sample of 2.4-dinitrobenzoic acid (m.p. 181–182°): 165–168° dec.

Reduction of II, III, and V to α-aminobenzylidene-γ-butyrolactones. Ninety grams of tin (II) chloride dihydrate (0.4 mole) were dissolved in 225 cc. of conc. hydrochloric acid and 14.8 g. (0.0675 mole) of V[2] (m.p. 142–145°) were added. Nearly the entire amount went into solution. After a few minutes a moderately exothermic reaction occurred and the mixture solidified. After 24 hours' standing at room temperature, the precipitate was filtered by suction, (still wet) immediately added to 300 cc. of a conc. aqueous solution of ammonia, and stirred for several hours at room temperature. The residue was filtered, washed thoroughly with water, and dried carefully. The brown-yellowish powder was then extracted with chloroform in a Soxhlet apparatus for about 24 hr. until the residue did not contain any more organic material.

The chloroform solution in which the amine VI partly had precipitated was evaporated to dryness and the yellow residue recrystallized from methanol, yielding 9.3 g of yellow leaflets, m.p. 164–165.5°. From the mother liquor, a second fraction (1.4 g., m.p. 161.5–162.5°) was obtained. Total yield: 10.7 g. (84%) of *α-(m-aminobenzylidene)-γ-butyrolactone* (*VI*).

An analytical sample melted at 163°.

Anal. Calcd. for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.86. Found: C, 69.73; H, 6.05.

The *hydrochloride*, after several recrystallizations from 95% ethanol, decomposed between 237 and 240°.

Anal. Calcd. for $C_{11}H_{12}ClNO_2$: C, 58.53; H, 5.36; N, 6.21. Found: C, 58.11; H, 5.45; N, 5.93.

Similarly, from 40.2 g. of II, a yield of 32.3 g. (93%) of *α-(p-aminobenzylidene)-γ-butyrolactone* (*VII*), m.p. 189–192°, was obtained. The analytical sample melted at 194–195.5°, yellow-brownish needles from 95% ethanol.

Anal. Calcd. for $C_{11}H_{11}NO_2$: N, 7.40. Found: N, 7.18.

Hydrochloride, m.p. 224–225.5° (from 10% aq. hydrochloric acid).

Anal. Calcd. for $C_{11}H_{12}ClNO_2$: Cl, 15.72. Found: Cl, 15.55.

Similarly, from 3.0 g. of III, 2.1 g. (81%) of *α-(o-aminobenzylidene)-γ-butyrolactone* (*VIII*), m.p. 147–149°, were obtained. The analytical sample, yellow plates from methanol, melted at 149–150°.

Anal. Calcd. for $C_{11}H_{11}NO_2$: N, 7.40. Found: N, 7.47.

Hydrochloride, m.p. 198–199° dec. (from 10% aq. hydrochloric acid).

Anal. Calcd. for $C_{11}H_{12}ClNO_2$: Cl, 15.72. Found: Cl, 15.72.

Hydrogenations of VI and VII. The hydrogenations were performed in methanol with platinum oxide as catalyst in a Parr apparatus as described earlier.[2] Since the uptake of hydrogen was rather slow, some heating was applied. In both cases, the reaction product solidified after evaporation of the methanol and was recrystallized from methanol-ether; from the mother liquors a second fraction was obtained.

Four grams of VI yielded thus 2.0 g. of a first fraction, m.p. 73–75°, and 0.3 g. of a second fraction, m.p. 69–73°, totaling 57% of *α-(m-aminobenzyl)-γ-butyrolactone*. The analytical sample melted at 73.5–75°.

Anal. Calcd. for $C_{11}H_{13}NO_2$: N, 7.33. Found: N, 7.53.

Similarly, an 81% yield of *α-(p-aminobenzyl)-γ-butyrolactone* was obtained from VII, m.p. 84.5–85.5° after 4 recrystallizations from methanol and methanol-ether, respectively.

Anal. Calcd. for $C_{11}H_{13}NO_2$: N, 7.33. Found: N, 7.44.

Amides of VI and VII (cf. Table I). The following derivatives have been prepared according to standard procedures[6] in high yields.

Reaction of I with chlorosulfonic acid. A solution containing 20 g. (0.115 mole) of I in 50 cc. of chloroform was prepared and cooled by means of an ice-salt mixture. No attention was paid to the partial reprecipitation of I that occurred. Chlorosulfonic acid (100 cc.) was added gradually with shaking and the mixture was kept in a stoppered bottle for 2 days at room temperature. It was then poured on ice. The resulting precipitate was filtered with suction and washed with large amounts of water until the washings were neutral. The crude product, after drying, weighed 20.5 g. and melted at 160–165° (157° sint.). The two layers of the filtrate were separated, the chloroform layer washed with water, and the solvent evaporated. A greyish residue remained which after putting on a clay plate and recrystallization from a small amount of dioxane gave additional 0.5 g. of material, m.p. 164–165.5°. Total yield: 21.0 g. of crude material (67%). Several recrystallizations from dioxane-ether raised the m.p. of the *α-(p-chlorosulfonylbenzylidene)-γ-butyrolactone* (*VIII*) to 171–172°. Small white leaflets.

Anal. Calcd. for $C_{11}H_9ClO_4S$: C, 48.45; H, 3.33; Cl, 13.00; S, 11.76. Found: C, 48.75; H, 3.43; Cl, 12.79; S, 11.76.

The compound can also, less satisfactorily, be recrystallized from ethyl acetate.

Reaction of VIII with ammonia. Five g. of VIII were kept for 48 hr. at room temperature with 100 cc. of conc. aqueous ammonia. The crystals dissolved slowly. On evaporation in an open porcelain dish (no heat), white crystals precipitated. These were filtered and washed with water, then with methanol and with ether; 0.6 g., m.p. 209–210.5°. The filtrate was evaporated to dryness, the residue treated with 5 cc. of water, filtered, and washed as above; 1.7 g., m.p. 210–211°. Total yield: 2.3 g. (49%). After several recrystallizations from methanol, the analytical sample of *α-(p-sulfonamidobenzylidene)-γ-butyrolactone* (*IX*) melted at 210–211°.

Anal. Calcd. for $C_{11}H_{11}NO_4S$: C, 52.16; H, 4.38; N, 5.53; S, 12.66. Found: C, 52.04; H, 4.36; N, 5.33; S, 12.36.

Oxidation of IX by 4 hr. refluxing with an aqueous solution of potassium permanganate gave *p*-sulfonamidobenzoic acid, dec. at 279° after one recrystallization from water (lit.[7]: dec. 280°).

Reaction of VIII with hydrazine. With stirring, 2.6 g. of VIII were added to a mixture of 5 cc. of 85% hydrazine hydrate and 5 cc. of water. The slightly exothermic reaction did not start until the reaction mixture was gently warmed on a water bath (40°) for a few minutes. After cooling with ice-water, a voluminous white precipitate was obtained which was filtered and washed with a small amount of water;

(6) 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, N. Y., 1956, pp. 103. 226.

(7) C. Palmer, *Am. Chem. J.*, **4**, 164 (1882).

1.5 g., m.p. 134–135° (dec.). Only oily substances which were discarded resulted on evaporation of the filtrate. After three recrystallizations from methanol (considerable loss of material:), *α-(p-hydrazidosulfonylbenzylidene)-γ-butyrolactone* decomposed at 159–160°.

Anal. Calcd. for $C_{11}H_{12}N_2O_4S$: C, 49.25; H, 4.59. Found: C, 49.19;H, 5.23.

Reaction of VIII with aniline. α-(p-Phenylamidosulfonylbenzylidene)-γ-butyrolactone was prepared according to standard procedures[6] and recrystallized from methanol-ether. M.p. 173–173.5° dec.

Anal. Calcd. for $C_{17}H_{16}NO_4S$: C, 61.99; H, 4.59. Found: C, 61.41, H, 4.85.

Acknowledgment. We appreciate the assistance of Mr. Jerome M. Sohmer and Mr. Horst Schmank who performed several of the experiments.

CINCINNATI 21, OHIO

Notes

A department for short papers of immediate interest.

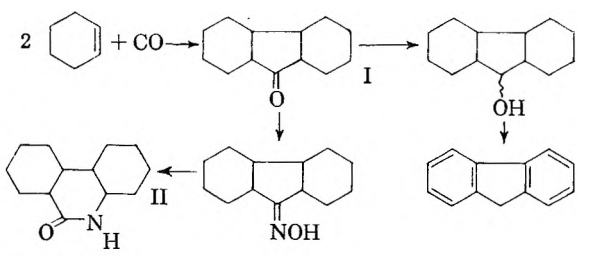
Thermal Carbonylation of Cyclohexene

PETER T. LANSBURY AND ROBERT W. MESCHKE

Received March 26, 1958

During the course of an investigation of certain carbonylation reactions, a mixture of cyclohexene, carbon monoxide, and hydrogen was processed in a stainless steel autoclave at 300° and about 800 atmospheres pressure. In addition to the normal hydroformylation products, hexahydrobenzaldehyde and cyclohexylcarbinol, a high-boiling carbonyl compound (I), b.p. 122.5–123°/5 mm., the elemental analysis of which corresponded to the formula $C_{13}H_{20}O$, was obtained in low yield. It seemed logical to assume that this material was dicyclohexyl ketone, arising from the addition of two moles of alkene to one mole of carbon monoxide and one mole of hydrogen.[1] However, further work (*vide infra*) revealed that I could be prepared by thermal reaction of cyclohexene and carbon monoxide only, and this, therefore, pointed to a perhydrofluorenone structure. We wish to present evidence favoring this structural assignment.

Compound I exhibited a carbonyl band in the infrared at 5.75 microns, indicative of a cyclopentanone-type ketone or an aldehyde[2] rather than a normal, unstrained ketone carbonyl. Furthermore, the oxime of I, which resisted recrystallization to a sharp melting point, also appeared to possess a five-membered ring containing the carbon-nitrogen double bond, as indicated by the $\diagdown C{=}N-$ infrared band at 5.95 microns,[3] and depressed the melting point of authentic dicyclohexyl ketoxime. These data suggested that I was a mixture of stereoisomeric perhydrofluorenones and that treatment with hydroxylamine yielded a mixture of isomeric oximes. In addition to analytical and spectral data in support of the proposed structure for I, the oxime was subjected to the Beckmann rearrangement in polyphosphoric acid and found to yield a lactam (II). II did not melt sharply, again indicating stereoisomers, but had the correct analysis and the expected infrared spectrum for a perhydrophenanthridone.[4] The possibility that I may have been an aldehyde, such as 2-cyclohexylhexahydrobenzaldehyde, was ruled out, since aldoximes generally give primary amides under these mildly acidic Beckmann conditions.[5] Moreover, spectral evidence (*vide supra*) contradicted the presence of a normal aldoxime group and I gave a negative Fehling's test. As a means of further identification I was reduced to perhydrofluorenol with lithium aluminum hydride and the crude product converted directly to fluorene by dehydrogenation over palladium.



Having established the novel nature of this reaction, efforts were directed toward defining optimum conditions for obtaining I. It was found that conventional carbonylation catalysts such as cobalt carbonyl did not affect the yield of I, and that best results could be achieved merely by processing cyclohexene and carbon monoxide at 350°C. for about eight hours (see experimental section). Although metal carbonyls were occasionally formed when the reaction was carried out in stainless steel autoclaves, the use of platinum-lined vessels was equally effective. This observation establishes the noncatalytic nature of the carbonylation. In the absence of hydrogen the normal hydroformylation products were not found. However, a hydrocarbon fraction, corresponding to (x)-cyclohexylcyclohexene[6] was obtained. Infrared data indicated that 1-cyclohexylcyclohexene was not a major component (little absorption at 11.9 to 12.7 microns).[7] The presence of 3- or 4-cyclohexylcyclohexene was suggested by a band attributable to *cis* unsaturation at 14.4 microns[7] in the infrared spectrum. Attempted hydrogenation of the cyclohexylcyclohexene fraction with palladized charcoal in a Parr hydrogenator yielded phenylcyclohexane and bicyclohexyl, resulting from a disproportionation *via* hydrogen transfer.[8] As expected, the cyclo-

(1) W. F. Gresham, R. E. Brooks, and W. E. Grigsby, U. S. Patent 2,473,995; G. Natta, P. Pino, and R. Ercoli, *J. Am. Chem. Soc.*, **74**, 4496 (1952).

(2) L. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley & Sons, New York, 1954, p. 114.

(3) L. Cross and A. Rolfe, *Trans. Far. Soc.*, **47**, 354 (1951).

(4) Ref. 2, pp. 176, 178.

(5) E. C. Horning and V. L. Stromberg, *J. Am. Chem. Soc.*, **74**, 5151, 5153 (1952).

(6) V. Mark and H. Pines, *J. Am. Chem. Soc.*, **78**, 5946 (1956).

(7) Ref. 2, p. 31.

(8) R. P. Linstead, E. A. Braude, P. W. D. Mitchell, K. R. H. Wooldridge, and L. M. Jackman, *Nature*, **169**, 100 (1952).

hexylcyclohexene can be obtained in the absence of carbon monoxide.[6] In two of the reactions of cyclohexene and carbon monoxide small amounts of fluorene were unexpectedly obtained. It is possible that under the rather strenuous reaction conditions simultaneous hydrogenation and dehydrogenation of I may yield fluorene.

The paucity of information relating to the pure stereoisomeric perhydrofluorenones precluded further attempts on our part along these lines. Whereas Linstead and coworkers[9] studied the pyrolysis of the six stereoisomeric perhydrodiphenic acids to perhydrofluorenones, the resolution of the resulting pyroketone mixtures into individual isomers was possible only by tedious separation of the mixed oximes. It appeared, however, that ketone I may be of the *syn*-series[9] since the melting points of the oxime and semicarbazone obtained from I correspond closely to the derivatives of the *syn*-pyroketone mixture.

In studying the scope of this reaction, cyclopentene and carbon monoxide yielded an analogous cyclic ketone, but no reaction occurred with a variety of aliphatic olefins.

EXPERIMENTAL

Boiling points and melting points are uncorrected. All infrared spectra were obtained using a Perkin-Elmer Model 21 double beam spectrometer.

Carbonylation of cyclohexene. A typical reaction involved the heating of 324 g. of cyclohexene at 350° for 6–8 hr. in a stainless steel autoclave under 700 atm. carbon monoxide pressure. Distillation of the pale yellow product gave several fractions having the following boiling point ranges: (1) 75–80°; *ca.* 200 g.; (2) 48–71°/3 mm., 4.6 g.; (3) 78–80°/3 mm., 23 g.; (4) 81–115°/3 mm., 6.0 g.; (5) 115°/3 mm., 23 g.; (6) 116–122°/3 mm., 11 g.; 30 g. pot residue. Fraction 1 was mainly unreacted cyclohexene with trace quantities of both benzene and cyclohexane as indicated by vapor phase chromatography using a column heated to 100°, with dinonyl phthalate supported on Celite as adsorbent, and helium as carrier gas.

Fraction 3, boiling point 78–80°/3 mm., n_D^{24} 1.4920–1.4928, was a clear mobile liquid. The infrared spectrum showed medium intensity bands at 3.3, 6.05, and 14.35 microns and little absorption at 11.9 to 12.7 microns. The presence of unsaturation was further indicated by the rapid decolorization of bromine in carbon tetrachloride. Hydrogenation of the olefin in absolute ethanol with 5% palladium on carbon at 25° and 60 p.s.i.g. in a Parr apparatus did not yield the anticipated bicyclohexyl. Instead, a mixture of bicyclohexyl and phenylcyclohexane, as confirmed by infrared analysis and vapor phase chromatography, was obtained.

Perhydrofluorenone (I). Fraction 5, boiling point 115°/3 mm. or 122.5–123°/5 mm., n_D^{24} 1.5038, was a clear, pale yellow, viscous liquid possessing a strong mint-like odor. The yield was approximately 6%. A strong absorption band at 5.75 microns was present in the infrared.

Anal. Calcd. for $C_{13}H_{20}O$: C, 81.1; H, 10.4. Found: C, 81.3; H, 10.6.

The *semicarbazone* of I was prepared[10] and after two recrystallizations from aqueous ethanol melted at 198–199°.

Anal. Calcd. for $C_{14}H_{23}ON_3$: C, 67.5; H, 9.3; N, 16.9. Found: C, 67.8; H, 9.4; N, 16.6.

The *oxime* was also prepared in the usual manner[10] and after several recrystallizations from aqueous methanol melted at 143–144.5°. (Another sample of oxime had m.p. 152–154° after three recrystallizations.) A mixed melting point with dicyclohexyl ketoxime, m.p. 163–163.5° (reported[11]: m.p. 158–159°), was 118–125°. Pertinent infrared spectral bands were found (KBr pellet) at 3.05 microns (strong: O—H stretching) and 5.95 microns (weak; $\rangle C{=}N-$ stretching). Authentic dicyclohexyl ketoxime shows $\rangle C{=}N-$ stretching at *ca.* 6.1 microns.

Anal. Calcd. for $C_{13}H_{21}OH$: C, 75.3; H, 10.2; N, 6.8. Found: C, 75.7; H, 10.2; N, 6.9.

A Beckmann rearrangement of the oxime was conducted by allowing 0.8 g. of oxime to stand overnight in 10 ml. of polyphosphoric acid and then warming on a steam bath for 1 hr. The burgundy-colored solution was diluted with water and 0.7 g. of solid material collected. This product after recrystallization from aqueous methanol gave white crystals, m.p. 164–165°. A strong band in the infrared spectrum (KBr pellet) was noted at 6.0 microns (lactam $\rangle C{=}O$) and weak bands were present at 3.15 and 3.25 microns (N—H stretching).

Anal. Calcd. for $C_{13}H_{21}ON$: C, 75.3; H, 10.2; N, 6.8. Found: C, 75.2; H, 10.2; N, 6.9.

For dehydrogenation of perhydrofluorenone to the aromatic parent, fluorene, I was first reduced to a carbinol. Approximately 2 g. of the ketone was added dropwise to excess lithium aluminum hydride in ether. After the initial vigorous reaction, the mixture was kept at room temperature overnight, cautiously treated with methanol, and then decomposed with 15% sulfuric acid. The ether layer was washed with 5% sodium bicarbonate solution and water, then dried over sodium sulfate. Removal of the ether by means of gentle heating under a stream of nitrogen left a colorless oil, which showed a strong infrared band at 2.9 microns and no carbonyl absorption. This material was heated for 2 hr. at 305° with 2 g. of 5% palladium-on-carbon, using nitrogen to sweep out the reaction tube. The mixture was extracted with hot ethanol; the solution was then filtered to remove catalyst and diluted with water to incipient crystallization. Cooling produced an initial crop (*ca.* 0.5 g.) of colorless solid, m.p. 109–111°, which, after recrystallization from methanol, melted at 113.5–114°. This material was identified as fluorene by comparing its infrared spectrum with an authentic sample, and a mixture melting point, which was undepressed.

Perhydrofluorenone (I) gave a negative Fehling's test and upon oxidation with alkaline permanganate gave an unresolvable mixture of acids.

Similar yields of cyclohexylcyclohexene and perhydrofluorene were obtained when platinum-lined autoclaves were employed and also when cobalt carbonyl was added as a catalyst.

Fluorene. In each of two reactions, as much as 3 g. of a white solid was obtained from the pot residues following distillation. Recrystallization from aqueous ethanol gave a product melting at 113–114°. Infrared comparison and a mixed melting point (no depression) with an authentic sample showed this material to be fluorene.

Carbonylation of cyclopentene. Employing the same procedure and conditions used with cyclohexene, cyclopentene (231 g.) was processed with carbon monoxide. A hydrocarbon, b.p. 46–48°/5 mm. and a ketone (15 g.; 5.4% yield), b.p. 99–99.5°/5 mm., were obtained. The former showed bands due to olefinic unsaturation at 3.3, 6.05, and 12.5

(9) S. B. Davis, W. E. Doering, P. Levine, and R. P. Linstead, *J. Chem. Soc.*, 1423 (1950).

(10) S. M. McElvain, *The Characterization of Organic Compounds*, Revised Edition, MacMillen Company, New York, 1953, p. 204.

(11) C. M. Hill and M. E. Hill, *J. Am. Chem. Soc.*, **75**, 2765 (1953).

microns, and a strong band at 5.78 microns was present in the spectrum of the ketone.

Anal. Calcd. for $C_{11}H_{16}O$: C, 80.5; H, 9.8. Found: C, 80.8; H, 9.7.

The colorless semicarbazone was prepared[10] and recrystallized from 25% ethanol, m.p. 188–189°.

Anal. Calcd. for $C_{12}H_{19}ON_3$: C, 65.2; H, 8.6. Found: C, 65.2; H, 8.6.

The 2,4-dinitrophenylhydrazone derivative formed as orange flakes, m.p. 144–145° (from 95% ethanol).

Anal. Calcd. for $C_{17}H_{20}O_4N_4$: C, 59.3; H, 5.8; N, 16.3. Found: C, 59.6; H, 6.0; N, 16.6.

Acknowledgment. The authors wish to thank Miss Barbara A. Montague for her assistance in interpreting the infrared spectra.

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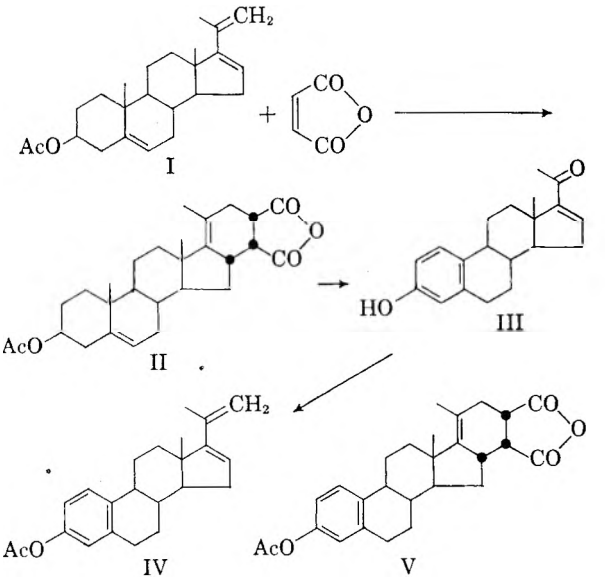
The Diels-Alder Reaction of Steroidal 20-Methylene-Δ^{16}-pregnene Derivatives with Maleic Anhydride

FRANZ SONDHEIMER AND RAPHAEL MECHOULAM

Received June 9, 1958

We have recently described[1] the synthesis of 20-methylene-$\Delta^{5,16}$-pregnadien-3β-ol acetate (I) by treatment of the corresponding 20-ketone with triphenylphosphine-methylene. The novel $\Delta^{16,20(22)}$-diene system present in I should permit its condensation with dienophiles in a Diels-Alder type of reaction to produce substances containing an additional ring (or rings) fused to the 16 and 17 positions of the steroid nucleus. Indeed when the triene I was allowed to react with maleic anhydride in boiling benzene, an adduct was obtained stereospecifically in excellent yield, which on the basis of the elemental analysis and spectral properties must be the pentacarbocyclic compound II. The β-configuration of the hydrogen substituent at C-16 is based on the expectation that attack of the dienophile proceeds from the less hindered α-side of I.[2] The β-hydrogen configuration at the other two new asymmetric centers follows from the rule of maximum accumulation of unsaturation in the transition state of the complex formed in the Diels-Alder reaction.[3]

In the 19-nor steroid series, 17-acetyl-$\Delta^{1,3,5(10),16}$-estratetraen-3-ol (III)[4] on treatment with triphenylphosphinemethylene and subsequent acetylation yielded the 19-nor-20-methylene-Δ^{16}-derivative IV, which was smoothly converted to the adduct V by means of maleic anhydride in boiling benzene. The Diels-Alder reaction between 20-methylene-Δ^{16}-pregnenes and maleic anhydride therefore appears to be general.[5]



EXPERIMENTAL[6]

Adduct II from 20-methylene-$\Delta^{5,16}$-pregnadien-3β-ol acetate (I) *and maleic anhydride.* A solution containing 100 mg. of the triene I (m.p. 124.5–126°)[1] and 100 mg. of freshly sublimed maleic anhydride in 10 cc. of dry benzene was boiled under reflux for 6 hr., cooled, and diluted with water. The organic layer was washed with 2% sodium hydroxide solution and water and was then dried and evaporated. The solid residue (108 mg.) showed m.p. 235–245° and after one crystallization from ether gave the analytical sample of the adduct II as needles with constant m.p. 255–256°, $[\alpha]_D$ −26°, ν_{max} 1860, 1780 cm.$^{-1}$ (5-membered cyclic anhydride) and 1735 cm.$^{-1}$ (acetate), no high-intensity absorption in the ultraviolet.

Anal. Calcd. for $C_{28}H_{36}O_5$: C, 74.30; H, 8.02. Found: C, 74.23; H, 7.88.

17-Isopropenyl-$\Delta^{1,3,5(10),16}$-estratetraen-3-ol acetate (IV) *from 17-acetyl-$\Delta^{1,3,5(10),16}$-estratetraen-3-ol* (III). A 1*N* ethereal solution of butyllithium (10 cc.) was added to a suspension of 3.57 g. (10 millimoles) of methyltriphenylphosphonium bromide in 50 cc. of ether with swirling under nitrogen. The mixture was shaken in nitrogen for 2 hr., and a solution of 590 mg. (2 millimoles) of 17-acetyl-$\Delta^{1,3,5(10),16}$-estratetraen-3-ol (III)[4] in 30 cc. of dry ether was then added. The mixture was shaken for a further 4 hr. and allowed to stand overnight at room temperature. Tetrahydrofuran was then added at the same time as the ether was distilled off until most of th latter had been replaced. The mixture was boiled

(1) F. Sondheimer and R. Mechoulam, *J. Am. Chem. Soc.*, **79**, 5029 (1957).

(2) *Cf.* L. F. Fieser, *Experientia*, **6**, 312 (1950).

(3) *Cf.* K. Alder and G. Stein, *Angew. Chem.*, **50**, 510 (1937).

(4) C. Djerassi, G. Rosenkranz, I. Iriarte, J. Berlin, and J. Romo, *J. Am. Chem. Soc.*, **73**, 1523 (1951).

(5) Since our work was completed, two patents have appeared describing the Diels-Alder reaction between 20-acetoxy-$\Delta^{16,20}$-pregnadiene derivatives and maleic anhydride [R. H. Mazur and G. P. Mueller, U. S. Patent **2,753,343**, July 3, 1956; *Chem. Abstr.*, **51**, 2070 (1957); R. H. Mazur, U. S. Patent **2,753,359**, July 3, 1956; *Chem. Abstr.*, **51**, 4436 (1957)].

(6) Melting points are uncorrected. Rotations were determined at 20–25° in chloroform solution. Ultraviolet spectra were measured on a Unicam Model S.P. 500 spectrophotometer and infrared spectra (in chloroform solution) on a Baird double beam recording spectrophotometer with sodium chloride prism. Analyses were carried out in our microanalytical laboratory under the direction of Mr. Erich Meier.

under reflux for 6 hr., cooled, and diluted with ether and water. The organic layer was washed with water, dried and evaporated to dryness. The residue was acetylated by being allowed to stand overnight at room temperature with 10 cc. of pyridine and 10 cc. of acetic anhydride. The product was isolated with ether in the usual way and chromatographed on 25 g. of Merck "acid-washed" alumina. The fractions eluted with petroleum ether-benzene (4:1) on crystallization from methanol yielded 290 mg. of the pentaene acetate IV with m.p. 118–120°. The analytical sample showed m.p. 132–133°, $[\alpha]_D$ + 65°, ν_{max} 1750 (phenyl acetate), 1620 and 890 cm.$^{-1}$ (terminal methylene), λ_{max} 239 mμ (log ϵ 4.22) (iso-octane).

Anal. Calcd. for $C_{23}H_{28}O_2$: C, 82.10; H, 8.39. Found: C, 82.11; H, 8.39.

Adduct V from 17-isopropenyl-$\Delta^{1,3,5(10),16}$-estratetraen-3-ol acetate (IV) *and maleic anhydride.* A solution of 60 mg. of the pentaene acetate IV and 60 mg. of maleic anhydride in 6 cc. of benzene was boiled under reflux for 6 hr. Isolation as previously and crystallization from ether gave 35 mg. of the adduct V with m.p. 178–182°. Further crystallization from ether gave the analytical specimen with m.p. 182–184°, $[\alpha]_D$ +83°, ν_{max} 1850, 1780 cm.$^{-1}$ (5-membered cyclic anhydride) and 1760 cm.$^{-1}$ (phenyl acetate), λ_{max} 268 mμ (log ϵ 2.98) (95% ethanol).

Anal. Calcd. for $C_{27}H_{30}O_6$: C, 74.63; H, 6.96. Found: C, 74.44; H, 7.02.

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Improved Yields in the Preparation of Diacetyl Peroxide

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Received June 16, 1958

In connection with some studies on the oxidation of cyclohexene[1] and on the stability of acyloxy radicals it was necessary to prepare reasonably large amounts of pure diacetyl peroxide in the solid state. The several methods of preparation available in the literature were found unsuitable. Thus, Shanley's method[2] is suitable for small amounts only, Walker's method[3] appeared too dangerous for large scale use, particularly in warm climates, and a patented method[4] involved an unsuitable solvent. The well-known method of Gambarjan,[5] outlined by Shirley[6] gave variable and poor yields. However, by modifying Gambarjan's method it was possible to prepare diacetyl peroxide in 79% yield, and the peroxide obtained was of excellent purity. Although Kuhn[7] recommends using the peroxide within 24 hours when it is prepared by Gambarjan's method, we were able to store the peroxide in Dry Ice and use it a week later. However, we do not recommend this as a general practice. Where it is necessary to prepare the solid peroxide for subsequent investigation in a particular solvent we recommend adding the solvent to the peroxide before removing the peroxide container from its Dry Ice surroundings.

EXPERIMENTAL

A solution of 87 g. (0.723 mole) acetic anhydride in 450 ml. of ether, freshly distilled after standing over sodium, was placed in a 1 liter Erlenmeyer flask in an ice bath. To the flask was added 43.5 g. (0.558 mole) of sodium peroxide in one portion. The mixture was stirred mechanically and distilled water (150 ml.) was added to it dropwise until all of the sodium peroxide had dissolved. The addition of the water took approximately 10 hr. and was controlled so as to keep the temperature of the mixture below 5° and to avoid, as much as possible, the evolution of oxygen. After the addition was finished the ether layer was separated and the aqueous layer was extracted with two 100-ml. portions of ether. The combined ether solutions were washed with two 100-ml. portions of 1% sodium bicarbonate solution to remove acetic acid. The ether solution was then dried over calcium chloride for 2 hr., carefully decanted into a tared, standard taper flask, which was equipped with a calcium chloride tube, and allowed to stand in a Dry Ice–alcohol slurry overnight. A large crop of solid peroxide crystals formed. This was not removed. Instead, the flask was raised slightly above the rim of the Dewar vessel, and the ether was removed at low pressure.

Iodimetric assay[8] gave a peroxide content of 98.97%. Small amounts of the solid peroxide were removed from the flask with a porcelain spatula for assay and quickly transferred to a weighing bottle containing a known weight of isopropyl alcohol. Large amounts of solid peroxide were *never* removed from the flask; instead the peroxide was dissolved in the required solvent and used in a manner to be described in a later publication.

Although this procedure takes longer than Gambarjan's[5] it has been found to be much more reliable and consistent in its results. For example, two representative runs using the quantities above gave 39.6 g. (79% yield) and 39.2 g. (77.8% yield), the yields being based on acetic anhydride. In contrast, by following Gambarjan's procedure, as described by Shirley,[6] yields varying from 9.1 to 43.3% were obtained in 5 attempts.

No trouble was experienced at any time during preparations as outlined above. During the removal of the ether by pumping and during storage and handling of the flask containing the solid peroxide the apparatus was shielded by safety screens. The solid was never allowed to approach its melting point and was never brought into contact with anything but glass or porcelain surfaces. Whenever possible the apparatus containing the solid peroxide was handled with tongs.

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(1) H. J. Shine and R. H. Snyder, *J. Am. Chem. Soc.*, **80**, 3064 (1958).
(2) E. S. Shanley, *J. Am. Chem. Soc.*, **72**, 1419 (1950).
(3) O. J. Walker, *J. Chem. Soc.*, 2040 (1928).
(4) H. A. Rudolph and R. L. McEwen, U. S. Patent **2,458,207** (to Buffalo Electric Co., Inc.), June 1949; *Chem. Abstr.* **43**, 3444 (1949).
(5) S. Gambarjan, *Ber.*, **42**, 4010 (1909).
(6) D. A. Shirley, *Preparation of Organic Intermediates*, J. Wiley and Sons, Inc., New York, N. Y., 1951, p. 1.
(7) L. P. Kuhn, *Chem. Eng. News*, **26**, 3197 (1948).
(8) C. D. Wagner, R. H. Smith, and E. D. Peters, *Ind. Eng. Chem., Anal. Ed.*, **19**, 979 (1947).

Stereochemistry of the Decomposition of 1,1-Dimethyl-2-phenylpropyl Hypochlorite[1]

DONALD B. DENNEY AND WILLIAM F. BEACH

Received June 18, 1958

The decomposition of tertiary alkyl hypochlorites proceeds in the following manner:

$$R_3C{-}O{-}Cl \longrightarrow R{-}\overset{\overset{O}{\|}}{C}{-}R + R{-}Cl$$

The reaction has considerable synthetic value as has been pointed out by Cairns and Englund.[2]

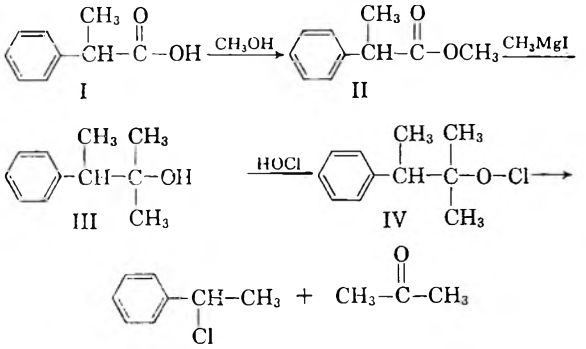
The gas phase decomposition of *t*-butyl hypochlorite has been studied by Yoffe[3], and he has suggested the following mechanism:

$$(CH_3)_3C{-}O{-}Cl \xrightarrow{\Delta} (CH_3)_3C{-}O\cdot + Cl\cdot$$

$$(CH_3)_3C{-}O\cdot \longrightarrow CH_3\cdot + CH_3{-}\overset{\overset{O}{\|}}{C}{-}CH_3$$

$$(CH_3)_3C{-}O{-}Cl + CH_3\cdot \longrightarrow (CH_3)_3C{-}O\cdot + CH_3{-}Cl$$

It seemed possible that some of the alkyl halide might be formed by an intramolecular process similar to that found for the decomposition of some peroxides.[4] In order to investigate this point, it was decided to study the sterochemistry of the decomposition. An intramolecular decomposition would lead to optically active halide of retained configuration. The reaction sequence started with (−)-hydratropic acid (I), which was converted



to (−)-methyl hydratropate (II). II was allowed to react with methylmagnesium iodide to afford the alcohol, III. A solution of III in carbon tetrachloride was allowed to react with hypochlorous acid to effect the conversion to the hypochlorite IV. Distillation of the carbon tetrachloride solution of IV afforded α-phenethyl chloride (V) and acetone, the expected products of the decomposition of IV.

The hydratropic acid used in this series had 47% of the possible optical activity. The α-phenethyl chloride isolated had 1.1% of the activity which could have been obtained by a stereospecific series of reactions. Although there may have been small amounts of racemization in the formation of II and III, the majority most probably occurred during the decomposition of III. Yoffe's mechanism predicts racemization during this reaction and these results support his mechanism.

The α-phenethyl chloride isolated from this reaction series had an observed rotation of + 0.69°. The alcohol, III, used in preparing the α-phenethyl chloride had an observed rotation of + 8.62°; all of the other compounds were levorotatory. If the rotation of the chloride is due to contamination by III, it must comprise 8% of the sample. A careful inspection of the infrared spectrum of the α-phenethyl chloride showed it to be identical to that of a known sample and it indicated that there was no III present.

It can be shown by a suitable combination of stereochemical data available in the literature[5] that (−)-hydratropic acid has the same absolute configuration as (+)-α-phenethyl chloride. This correlation shows that the small amount of optically active halide present is of the same configuration as the starting acid. This small amount of retention of configuration may have arisen by an intramolecular decomposition or by combination of an unracemized α-phenethyl radical and a chlorine atom in a solvent cage. It is clear though that the most favorable reaction path is not stereospecific and is best represented by Yoffee's mechanism.

EXPERIMENTAL

(−)-*Methyl hydratropate* (II). A solution of 47.0 g. (0.313 mole) of (−)-hydratropic acid, $[\alpha]_D^{21}$ −37.8° (lit.[6] $[\alpha]_D^{25}$ −81.10), in 190 ml. of methanol and 4 ml. of concentrated sulfuric acid was refluxed for 4 hr. Methanol, 145 ml., was removed by distillation and the residue was poured into 200 ml. of water. The ester was taken up in ether. The ether was extracted with a solution of potassium carbonate and then dried over anhydrous sodium sulfate. Distillation afforded 46.6 g. (87%) of (−)-methyl hydratropate, b.p. 71–75° (4.5 mm.), n_D^{25} 1.5012 (lit.[7] n_D^{18} 1.5008), α_D^{21} −44.5° (1 = 1 dm.).

Preparation of (+)-*1, 1-dimethyl-2-phenylpropan-1-ol* (III). To a solution of methylmagnesium iodide in ether prepared from 154 g. (1.085 mole) of methyl iodide and 26.4 g. (1.085 mole) of magnesium was added 44.5 g. (0.271 mole) of II in 100 ml. of dry ether. After the addition was completed, the reaction mixture was allowed to reflux for 2 hr. with stirring. The reaction mixture was treated with an aqueous ammonium chloride solution and then dried over

(1) Taken from a dissertation submitted by William F. Beach in partial fulfillment of the requirements for the degree of Bachelor of Science in Chemistry, Rutgers, The State University.

(2) T. L. Cairns and B. E. Englund, *J. Org. Chem.*, 21, 140 (1956).

(3) A. D. Yoffe, *Chem. & Ind. (London)*, 963 (1954).

(4) C. Walling, *Free Radicals in Solution*, John Wiley and Sons, New York, N. Y., 1957, p. 501–503.

(5) W. Klyne, *Progress in Stereochemistry*, Butterworths Scientific Publications, London, 1954, p. 187.

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sodium sulfate. Distillation afforded 44.7 g. (88%) of (+)-1, 1-dimethyl-2-phenylpropan-1-ol, b.p. 78–84° (5 mm.) n_D^{23} 1.5147 (lit.[7] n_D^{22} 1.5162), α_D^{23} +8.62° (1 = 1 dm.).

Preparation and decomposition of 1,1-dimethyl-2-phenylpropyl hypochlorite. A solution of 10.0 g. (0.0606 mole) of III in 50 ml. of carbon tetrachloride was stirred with 1200 ml. of 0.3 *M* hypochlorous acid solution[8] for 3 hr. at 0°. The yellowish-green carbon tetrachloride solution was separated, washed with water, and dried over calcium chloride. The carbon tetrachloride was removed under reduced pressure. The infrared spectrum of the carbon tetrachloride solution indicated the presence of a carbonyl compound, presumably acetone. The residue was distilled to yield 4.5 g. of material, b.p. 73–78° (11 mm.), n_D^{23} 1.5248, α_D^{26} +0.69° (1 = 1 dm.) (lit.[9] α_D^{25} 126°). The infrared spectrum of this material was identical to that of a known sample of α-phenethyl chloride.

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(8) R. Fort and L. Denivelle, *Bull. soc. chim. France*, 21, 1104 (1954).

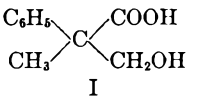
(9) R. L. Burwell, Jr., A. D. Shields, and H. Hart, *J. Am. Chem. Soc.*, 76, 908 (1954).

A Convenient Synthesis of α-Methyltropic Acid

ALBERTO VECCHI AND GAETANO MELONE

Received June 24, 1958

A synthesis of α-methyltropic acid (I) has been recently reported by Zaugg and DeNet.[1]

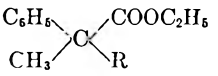


I

However, according to these authors, when α-phenylpropionic acid was treated with formaldehyde under the conditions of the Ivanov reaction, α-methyltropic acid was obtained in only trace amounts. Dimethyldiphenylsuccinic anhydride was the main end product, although yields were generally poor.

An attempted synthesis by the action of nitrous acid on ethyl β-amino-α-methyl-α-phenylpropionate[2] failed to give the expected compound, since rearrangement occurred with formation of α-benzyllactic acid.[3]

We have now ascertained that α-methyltropic acid may be prepared in reasonable yield through a way already described by Fusco and Testa for α-ethyltropic acid.[4] The starting compound was diethyl phenylmethylmalonate[5] (II), which was partially hydrolyzed to the monoester (III) in an alcohol solution of potassium hydroxide at room temperature. The monoester was then converted into the ester-chloride (IV) by reaction with thionyl chloride. Reduction of the acyl chloride with sodium borohydride gave the alcohol-ester (V), which was finally hydrolyzed to the free acid.



II. R = $COOC_2H_5$
III. R = COOH
IV. R = COCl
V. R = CH_2OH

The over-all yields ranged between 26 and 28%, based on the starting diethyl phenylmethylmalonate.

(1) H. E. Zaugg and R. W. DeNet, *J. Org. Chem.*, 23, 498 (1958).

(2) R. Foster and H. R. Ing., *J. Chem. Soc.*, 938 (1956).

(3) R. Foster and H. R. Ing., *J. Chem. Soc.*, 925 (1957).

(4) R. Fusco and E. Testa, *"Il Farmaco" Sci.*, 12, 3 (1957).

(5) W. Wislicenus and K. Goldstein, *Ber.*, 28, 815(1895).

EXPERIMENTAL

Monoethyl phenylmethylmalonate (III). To a solution of 37.8 g. of potassium hydroxide in 250 ml. of water and 700 ml. of ethyl alcohol, 117.6 g. of diethyl phenylmethylmalonate was added quickly with stirring and the mixture was allowed to stand for about 100 hr. at room temperature. After this time hydrochloric acid was added to *p*H about 7.0, the ethyl alcohol was distilled off under reduced pressure, and the residue was diluted with an equal volume of water. After extraction with ethyl ether of some unreacted diethyl ester, the water layer was made acidic to *p*H 3–3.5 with hydrochloric acid. The separated oil was extracted with ethyl ether and the solvent removed *in vacuo;* the residue was sufficiently pure for the following step.

α-Phenyl-α-carbethoxypropionyl chloride (IV). The above crude ester (81 g.) was mixed cautiously with 81 ml. of thionyl chloride and refluxed for 2 hr. The excess thionyl chloride was then removed under reduced pressure. Distillation of the residue yielded 57.5 g. (66% based on the crude monoester) of IV, b.p. 135–136° (5 mm.).

Ethyl α-phenyl-α-hydroxymethylpropionate (V). To a well stirred suspension of 13.4 g. of sodium borohydride in 135 ml. of anhydrous dioxane a solution of 57.5 g. of IV in 250 ml. of anhydrous dioxane was added slowly in about 1 hr. Then the mixture was refluxed for 2.5 hr. on an oil bath. After cooling the mixture was cautiously poured into 500 ml. of ice water, taking care that the temperature did not exceed 25°. Hydrochloric acid was added to *p*H about 4, then the mixture was extracted with four 200-ml. portions of ethyl ether. The combined ether extracts were washed to neutral reaction and the solvent was removed *in vacuo*. The residue was distilled in a Claisen flask collecting at 130–132° (2 mm.); clear colorless oil. Yield 36 g. (72%).

α-Methyltropic acid (I). The above ester V (36 g.) was hydrolyzed by refluxing it for 5 hr. under rapid stirring with 720 ml. of 10% aqueous sodium hydroxide. After cooling the mixture was extracted with ethyl ether, the aqueous layer was made acidic to Congo red with hydrochloric acid, and the separated oil was extracted with ethyl ether. The solvent was removed *in vacuo* and the oily residue dissolved in equal volume of anhydrous benzene. The benzene solution was poured with stirring and cooling into 5 volumes of petroleum ether. An oil precipitated which crystallized after prolonged stirring and cooling. The white crystals were collected, washed with petroleum ether, and dried *in vacuo*. Yield 21.5 g. (70%); m.p. 86–87°.

Anal. Calcd. for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.28; H, 6.80.

Acidimetric assay: 99%. The infrared spectrum was entirely consistent with the formula. After a further crystal-

lization from ligroin the product melted at 91–92°. Mixed melting point with an authentic sample of α-benzyllactic acid (m.p. 98°) was depressed to 67–68°.

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Zinc Complex of Toluene-3,4-dithiol as a Reagent for Ketose Sugars

ROBERT E. D. CLARK AND ROY G. NEVILLE[1]

Received June 25, 1958

Aliphatic and aromatic aldehydes and ketones react readily with 1,2-dimercapto compounds to form cyclic derivatives which are often intensely colored or easily oxidized to intensely colored compounds. Thus 1,2-dimercaptobenzene, I, condenses with benzaldehyde to give II which, in turn, is easily oxidized to salts of the cation III.[2] Similarly, 1,2-dimercaptoethane is a well recognized reagent for ketones.[3,4] In view of these facts it might be expected that the commercially available toluene-3,4-dithiol ("dithiol"), IV, would likewise afford a useful reagent for aldehydes and ketones.[5]

The poor keeping qualities of dithiol make it a difficult reagent to use. Recently, however, it has been found that its colorless zinc derivative, "zinc dithiol," V (or possibly VI), is surprisingly stable.[6] This is now available[1] as a very bulky pure white powder, the marked non-wettability of which appears to protect it from attack even on considerable exposure to acid vapors. It can generally be used in place of free dithiol and has application in the testing for trace quantities of numerous cations.[7]

It has been found that most common aldehydes do in fact react to give yellow colorations, or oily precipitates, when warmed with zinc dithiol in acid solution. Of immediate interest, however, is a reaction which occurs with sugars. When fructose or sorbose in dilute hydrochloric acid solution is heated to boiling with zinc dithiol a strong yellow color begins to develop within a few seconds and, after about 60 seconds, an oily yellow or orange precipitate separates. With sucrose a similar color develops, but much more slowly, doubtless owing to hydrolysis with formation of fructose. Among the sugars it appears that the reaction is given only by ketoses. In 4*N* hydrochloric acid none of the following available sugars or related compounds was found to give a reaction: arabinose, citric acid, galactose, glucose, inositol, lactose, mannitol, mannose, raffinose,[8] rhamnose, tartaric acid, xylose. Furfural gave a pale yellow color, much less intense than that given by the ketoses. In 2*N* acid the same distinction was observed, but the rate of development of color with fructose and sorbose was rather slow.

The reaction affords a quick and easy method by means of which ketoses may be immediately distinguished from aldoses. For example, fructose may be distinguished from glucose, or may be detected in the presence of the latter. The test is easily applied to qualitative work since neither the exact concentration of the acid nor the relative proportions of the reactants are critical. Since, under the conditions of the experiment, dithiol does not combine with such sugars as glucose, and since the excess of dithiol present may readily be titrated with mercuric chloride in presence of pyridine with a trace of a cobalt salt as indicator,[6] it appears that the reaction could be adapted to the quantitative estimation of ketoses.

This method was compared with others previously described for the detection of ketose sugars (8, 9). Although the anthrone reagent of Johanson is effective for developing chromatograms, and in spot test analysis, for qualitative identification in solution it was found to be inferior to dithiol. For example, addition of anthrone reagent to a dilute solution of fructose required three minutes for the color to develop, whereas less than 25 seconds was required for a strong yellow coloration employing the zinc complex of IV. The final color intensity and the sensitivity appeared to be of the same order of magnitude for both methods.

EXPERIMENTAL

General procedure for sugar analysis. To 0.25 ml. of dilute hydrochloric acid[10] was added 0.3–0.5 mg. (or more) of the sugar to be tested together with approximately the same amount of zinc dithiol. The mixture was heated to boiling, with shaking, and held at the boiling point for 30–60 sec. In presence of a ketose the liquid begins to become yellow within a few seconds, with deposition of a yellow or orange-yellow precipitate within 0.5–2.0 min., depending upon the concentration. With sucrose the color develops more slowly but is easily visible within 30–60 sec. The precipitate is readily visible when formed in a 0.2% fructose solution.

Comparison of anthrone with zinc dithiol in detection of fructose. Anthrone reagent was prepared by the method of Johanson.[9] Three min. was required for color to develop when fructose (1.0 mg.) was added to 0.25 ml. of reagent. Using zinc dithiol a strong yellow color developed within 25 sec. in presence of 0.5 mg. fructose. The final color intensities and sensitivities appeared to be comparable for both rea-

(1) Reprints of this article, diacetyl-3,4-dithiol, dibenzoyl-3,4-dithiol, and the zinc complex of toluene-3,4-dithiol are available from Dr. Roy G. Neville, 783 Cereza Drive, Palo Alto, Calif.

(2) W. R. H. Hurtley and S. Smiles, *J. Chem. Soc.*, 534 (1927).

(3) H. Hauptmann, *J. Am. Chem. Soc.*, **69**, 562 (1947).

(4) L. F. Fieser, *J. Am. Chem. Soc.*, **76**, 1945 (1954).

(5) W. H. Mills and R. E. D. Clark, *J. Chem. Soc.*, 175 (1936).

(6) R. E. D. Clark, *Analyst*, **82**, 182 (1957).

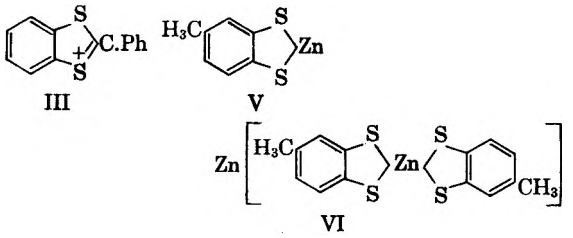
(7) R. E. D. Clark, *Analyst*, **61**, 242 (1936); **82**, 177, 760 (1957); **83**, 103, 396, 431 (1958).

(8) H. W. Rabin, *J. Am. Chem. Soc.*, **55**, 2603 (1933); **59**, 1402 (1937).

(9) R. Johanson, *Nature*, **172**, 956 (1953).

(10) One volume of concentrated hydrochloric acid diluted with 2 vol. of water.

gents. The solid sugar is required when using anthrone as this reagent must be employed in the presence of very little water. With zinc dithiol an aqueous solution of the sugar may be used.



III V VI

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Synthesis of 4-Acetylphenylmethylsilanes Using 2-(4-Bromophenyl)-2-methyl-1,3-dioxolane

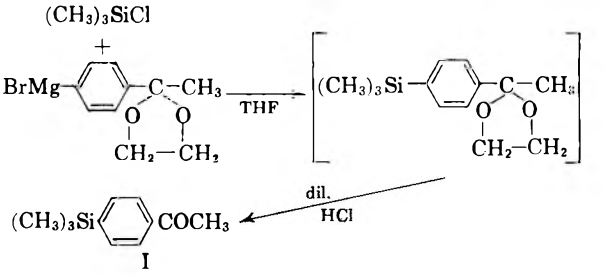
ROY G. NEVILLE[1]

Received July 28, 1958

When acylation of trimethylphenylsilane is conducted under the usual Friedel-Crafts conditions the aryl-silicon bond is cleaved by the aluminum chloride used as catalyst.[2,3] This fact has limited the availability of 4-trimethylsilylacetophenone (I), and similar acetyl compounds of silicon.

Recently, Szmant and Skendrovich[4] obtained approximately 35% yields of I using a modification of the Friedel-Crafts reaction in which trimethylphenylsilane is treated with acetyl fluoride in chloroform saturated with boron trifluoride. Apart from the low yield, the method is disadvantageous in that acetyl fluoride boils at room temperature and requires special care in handling to achieve the maximum reaction.

Continuing our work on organosilanes,[5] in this paper we wish to report that yields of I approximating 80% may be obtained by avoiding a Friedel-Crafts reaction. The Grignard reaction of the ethylene ketal of 4-bromoacetophenone, *i.e.*, 2-(4-bromophenyl)-2-methyl-1,3-dioxolane, with trimethylchlorosilane produces I in excellent yield. In addition to the high over-all yield this method offers the advantage that the acetyl substituent is in a known position. The possibility of isomeric contaminants, as in the Friedel-Crafts procedure, is thereby eliminated. The reaction occurs smoothly



in tetrahydrofuran, but attempts to form the Grignard reagent of the ketal in diethyl ether were unsuccessful.

The method has been extended to the preparation of the new compound di(4-acetylphenyl)dimethylsilane[6] in 50–60% yield. New derivatives of these compounds have also been prepared and are reported here.

EXPERIMENTAL

2-(4-Bromophenyl)-2-methyl-1,3-dioxolane (II). In a 3-l. flask, fitted with a Dean-Stark trap and reflux condenser, were placed 4-bromoacetophenone[7] (300 g., 1.5 moles), anhydrous ethylene glycol (93 g., 1.5 moles), 4-toluenesulfonic acid (1.2 g.), and anhydrous benzene (1500 ml.). The mixture was heated at brisk reflux until no more water distilled (20–25 hr.). Sodium acetate (1.2 g.) was added and the mixture stirred or shaken for 30 min., then filtered. The filtrate was washed thoroughly with water and dried over anhydrous sodium sulfate, and the benzene was distilled off at atmospheric pressure. The ketal was obtained as 300 g. (82%) of a colorless liquid, b.p. 175–180°/20–30 mm., which crystallized on standing in the receiver, m.p. 44–45°.[8] The infrared spectrum of the freshly prepared compound has a doublet at 1038 and 1078 cm.$^{-1}$ (C—O of a ketal) with no absorption in the carbonyl region.[9]

Anal. Calcd. for $C_{10}H_{11}BrO_2$: C, 49.34; H, 4.56; Br, 32.87. Found: C, 49.10; H, 4.51; Br, 32.90.

Hydrolysis of the ketal in the standard manner yielded 4-bromoacetophenone, m.p. 50°, which was characterized by its phenylhydrazone, m.p. 125°.[10]

4-Trimethylsilylacetophenone (I). Magnesium turnings (40 g., 1.65 g. atom), methyl iodide (5 ml.), and sodium-dried tetrahydrofuran (THF, 600 ml.), were placed in a 5-liter flask fitted with reflux condenser, motor-driven stirrer, thermometer, and dropping funnel. The mixture was heated at gentle reflux on the water bath and, after the methylmagnesium iodide had formed, a solution of the ketal (II) (334 g., 1.38 moles) dissolved in anhydrous THF (400 ml.) was run in, dropwise, during a period of about one hour. Gentle reflux was maintained for a further hour, then trimethylchlorosilane (150 g., 1.38 moles) was added with stirring to the solution cooled to 40°. After refluxing for an hour the mixture was allowed to cool overnight then 2 l. of water (containing 100 ml. of concentrated hydrochloric acid) was added to dissolve the crystalline magnesium salts. The lower aqueous layer was separated and the yellow oil was first washed several times with saturated calcium chloride

(1) For reprints: 783 Cereza Drive, Palo Alto, Calif.

(2) W. E. Evison and F. S. Kipping, *J. Chem. Soc.*, 2774 (1931).

(3) The phenyl-silicon bond of trimethylphenylsilane is also cleaved by bromine. See R. A. Benkeser and A. Torkelson, *J. Am. Chem. Soc.*, **76**, 1252 (1954).

(4) H. H. Szmant and S. Skendrovich, *J. Am. Chem. Soc.*, **76**, 2282 (1954).

(5) R. G. Neville, *J. Org. Chem.*, **23**, 937 (1958).

(6) Other acetylphenylsilanes are currently being synthesized in these laboratories.

(7) R. Adams and C. R. Noller, *Org. Syntheses*, Coll. Vol. I, 2nd edition, 109 (1951).

(8) All melting points are uncorrected.

(9) H. O. House and J. W. Blaker, *J. Org. Chem.*, **23**, 335 (1958).

(10) A. I. Vogel, "A Text-book of Practical Organic Chemistry," Longmans, Green and Co., London, 1956, p. 743.

solution,[11] then with water. After drying the oil over sodium sulfate the fraction of b.p. 150–175°/40–50 mm. was collected as a colorless liquid which solidified to 220 g. (83%) of white prisms, m.p. 41°.

Anal. Calcd. for $C_{11}H_{16}OSi$: C, 68.72; H, 8.39. Found: C, 68.99; H, 8.27.

This compound was characterized as the semicarbazone, oxime, phenylhydrazone, and 2,4-dinitrophenylhydrazone.

4-Trimethylsilylacetophenone semicarbazone. This derivative was formed in the standard manner. Two recrystallizations from isopropyl alcohol yielded colorless needles, m.p. 221°.

Anal. Calcd. for $C_{12}H_{19}N_3OSi$: N, 16.85. Found: N, 16.82.

4-Trimethylsilylacetophenone oxime. To a solution of hydroxylamine hydrochloride (5 g.) in water (10 ml.) were added I (12.8 g.) and a solution of sodium hydroxide (3 g.) in water (5 ml.). Isopropyl alcohol was cautiously added until, on warming to about 70°, the solution became clear and free from insoluble droplets. The mixture was heated at reflux on the water bath for 4 hr., then poured into water (100 ml.), and allowed to crystallize overnight. The stubby prismatic crystals were filtered, washed with water, and drained, m.p. 90–91°. Yield, 13.7 g. (99%). Two recrystallizations from alcohol raised the m.p. to 92°.

Anal. Calcd. for $C_{11}H_{17}NOSi$: N, 6.76. Found: N, 6.74.

4-Trimethylsilylacetophenone phenylhydrazone and 2,4-dinitrophenylhydrazone. The phenylhydrazone was prepared by the same procedure as that employed for acetophenone phenylhydrazone.[12] Recrystallization from alcohol yielded very pale yellow needles, m.p. 93°. On standing at room temperature for two to three days the crystals darkened considerably and began to decompose. It is well known that the acetophenone derivative behaves similarly.

The *2,4-dinitrophenylhydrazone*[4] was prepared in the usual manner and melted at 195°.

Anal. Calcd. for $C_{17}H_{20}N_4O_4Si$: N, 15.05. Found: N, 14.94.

Di(4-acetylphenyl)dimethylsilane. This compound was prepared in a manner similar to that employed for the preparation of I, using the following amounts of reactants: magnesium turnings (60 g., 2.47 g. atoms), ketal (II) (486 g., 2.0 moles), dimethyldichlorosilane (129 g., 1.0 mole). After addition of dilute hydrochloric acid, ether extraction and washing with saturated calcium chloride followed by water, the ether solution was dried over sodium sulfate, then distilled. The colorless liquid (172 g., 58%) of b.p. 287–290°/40 mm. was collected and crystallized in the receiver. Two recrystallizations from alcohol gave white needles, m.p. 130°.

Anal. Calcd. for $C_{18}H_{20}O_2Si$: C, 72.95; H, 6.80. Found: C, 72.77; H, 6.58.

Di(4-acetylphenyl)dimethylsilane disemicarbazone was prepared in the usual manner. Recrystallization from alcohol gave white needles, m.p. 137°.

Anal. Calcd. for $C_{20}H_{26}N_6O_2Si$: N, 20.48. Found: N, 20.37.

Acknowledgment. The author thanks Mr. Richard G. Tonkyn for helpful discussions concerning this work. Thanks are also due to Miss Ethel Schiavon and Mr. Joseph Wirth for their experimental assistance.

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(11) A stable emulsion results if water is used as the first wash liquid.

(12) H. Reisenegger, *Ber.*, 16, 662 (1883); R. L. Shriner, W. C. Ashley, and E. Welch, *Org. Syntheses*, Coll. Vol. III, 726, (1955); F. G. Mann and B. C. Saunders, "Practical Organic Chemistry," Longmans, Green and Co., London, 1949, p. 177.

Alkali Metal Complexes of Phenylalanine Derivatives[1,2]

MURRAY GOODMAN AND KENNETH C. STUEBEN

Received June 30, 1958

During the course of our work on the synthesis of peptides, we noted disagreement in the literature as to the correct melting point of benzyloxycarbonyl-L-phenylalanine. Bergmann[3] and Smith[4] reported 126–128° for the L- and D-isomers respectively but Holley[5] pointed out that this material possessed abnormally high neutralization equivalents. In addition, Holley[5] found that the neutralization equivalent could be lowered considerably by treating the product with dilute hydrochloric acid. Recently, Kenner[6] and coworkers, employing countercurrent distribution, were able to isolate a fraction which had the correct neutralization equivalent and melted at 87°. In this communication we wish to report that the high melting materials previously isolated were complexes of benzyloxycarbonyl-L-phenylalanine with its sodium salt. Conclusive evidence for the nature of these complexes was initially obtained in our laboratories using the DL-isomer.

When we prepared benzyloxycarbonyl-DL-phenylalanine, we observed the appearance of a side product which melted at 168°, much higher than the recorded 103° of the desired product. Elemental analyses, molecular weight, and infrared spectra indicated that the side product was a 1:1 complex of benzyloxycarbonyl-DL-phenylalanine with its sodium salt. This substance was subsequently shown to be identical with that obtained by half-neutralizing a sample of the pure acid with standard sodium hydroxide.

In the case of the corresponding L-isomer the product prepared in the usual way consists of varying quantities of the free acid and its sodium salt as evidenced from the neutralization equivalents reported.[5,6] These crude products can be converted to pure benzyloxycarbonyl-L-phenylalanine melting at 87° by extended treatment with hydrochloric acid. It is possible, however, to isolate a substance corresponding almost exactly to a 1:1 complex by acidifying the Schotten-Baumann reaction mixture to *p*H 5. Further acidification

(1) Presented before the Organic Section of the American Chemical Society at the 133rd meeting, San Francisco, Calif., April 1958.

(2) This research was supported by a grant from the National Science Foundation.

(3) M. Bergmann, L. Zervas, H. Rinke, and H. Schleich, *Z. physiol. chem.*, 224, 33 (1934).

(4) C. S. Smith and A. E. Brown, *J. Am. Chem. Soc.*, 63, 2605 (1941).

(5) R. W. Holley and A. D. Holley, *J. Am. Chem. Soc.*, 74, 3069 (1952).

(6) D. W. Clayton, J. A. Farrington, G. W. Kenner, and J. M. Turner, *J. Chem. Soc.*, 1398 (1957).

results in the precipitation of additional quantities of the carboxylic acid but the crude product is invariably mixed with some of the sodium complex. Furthermore, if the pure acid is half-neutralized with sodium hydroxide it can be reconverted to a complex which melts at 129.5–132°. This complex appears to be less stable than the analogous DL-complex since numerous attempts at recrystallization led to partial decomposition. These partially decomposed materials have the melting points of 126–128° reported by Bergmann[3] and Smith.[4]

The effect of other blocking groups and cations on the complex formation were examined briefly. Formyl-DL-phenylalanine and a dipeptide derivative (benzyloxycarbonylglycyl-L-phenylalanine) also exhibit the ability to form complexes. In the case of benzyloxycarbonyl-DL-phenylalanine, it was possible to isolate a solid potassium containing complex but the analogous lithium compound was obtained as a mixture of oil and solid.

EXPERIMENTAL[7,8]

Preparation of benzyloxycarbonyl-DL-phenylalanine and isolation of the complex. Benzyloxycarbonyl-DL-phenylalanine was prepared according to the standard procedure.[9] The crude product was dissolved in 550 ml. of hot ethyl acetate. On storage, 2.0 g. of a substance crystallized, m.p. 168–170°. Concentration of the filtrate to 75 ml. yielded an additional 4.1 g., m.p. 168–169.3°. Further concentration of the filtrate gave only benzyloxycarbonyl-DL-phenylalanine, m.p. 101–103.6°.

The combined 6.1 g. of high melting material was recrystallized several times from ethyl acetate, m.p. 168.5–169°.

Anal. Calcd. for $C_{34}H_{33}N_2O_8Na$: C, 65.89; H, 5.36; N, 4.51; Na, 3.70; mol. wt. 620.6; neut. equiv. 620.6. Found: C, 65.68; H, 5.53; N, 4.76; Na, 3.76; mol. wt. 656 (isothermal distillation in methanol); neut. equiv. 622.

Benzyloxycarbonyl-L-phenylalanine was prepared in the usual manner,[3] with the following modification. Rather than precipitating the product as a solid by acidification, the alkaline solution was acidified and extracted with ether. The ethereal solution was then washed with 2*N* hydrochloric acid, water, dried, and evaporated to give a solid which melted at 85.5–86.2°, after one crystallization from ethyl acetate-petroleum ether. One more crystallization gave m.p. 86.5–87.5°, $[\alpha]_D^{23}$ +5.2° (C 5.2, HOAc). (lit.[6] m.p. 87°, $[\alpha]_D^{18}$ +5.3° (±0.2) (C 6.6, HOAc).

Anal. Calcd. for $C_{17}H_{17}NO_4$: C, 68.40; H, 5.70; N, 4.69. Found: C, 68.43; H, 5.67; N, 4.79.

Isolation of sodium complex of benzyloxycarbonyl-L-phenylalanine. The alkaline solution resulting from the Schotten-Baumann acylation of L-phenylalanine with benzyloxycarbonyl chloride was acidified to *p*H 5. The precipitate which formed was removed by filtration, m.p. 132.5–133.5°. This solid was analyzed directly after drying at 120° for two days *in vacuo*.

Anal. Calcd. for $C_{34}H_{33}N_2O_8Na$: C, 65.89; H, 5.36; N, 4.51; Na, 3.70. Found: C, 65.98; H, 5.45; N, 4.62; Na, 2.79.

Preparation of the sodium complex of benzyloxycarbonyl-DL-phenylalanine. A solution of 0.5009 g. (0.00168 mole) of benzyloxycarbonyl-DL-phenylalanine in aqueous ethanol was half-neutralized with 8.4 ml. of 0.100*N* sodium hydroxide. Evaporation of the solvent under reduced pressure and drying in vacuo yielded a crystalline solid which melted at 165–167°. After recrystallization from ethyl acetate the material melted at 168–168.3°. A mixed melting point determination with the original complex (m.p. 168.5–169° isolated previously) melted at 168–168.7°. Also, the infrared spectrum was identical with that obtained from the original complex.

Preparation of other complexes. In a fashion similar to that described above, several other amino acid derivatives were treated with one-half equivalent of standard base and the products isolated by evaporation. The data are summarized in Table I.

TABLE I
1:1 COMPLEXES FORMED BY HALF NEUTRALIZATION[a]

Original Compound	M.P.	Treated with One-half Equiv. of	M.P. of Product
Benzyloxycarbonyl-L-phenylalanine	87°	NaOH	129.5–132°
Benzyloxycarbonyl-DL-phenylalanine	102°	KOH	179.2–180.5°
Benzyloxycarbonyl-DL-phenylalanine	102°	LiOH	Mixture of oil and crystals
Benzyloxycarbonyl-glycyl-L-phenyl-alanine	122°	NaOH	160–164.8°
Formyl-DL-phenyl-alanine	167°	NaOH	204–206° dec.

[a] These materials have been shown to contain no water of hydration by Karl-Fischer titration.

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(7) All melting points are uncorrected.

(8) Microanalyses by Schwarzkopf Laboratories, Woodside, N. Y.

(9) M. Bergmann and L. Zervas, *Ber.*, 65, 1192 (1932).

A Synthesis of 2-Amino-6-trifluoromethylpurine

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In the course of metabolite antagonist studies, 2-amino-6-trifluoromethylpurine was required for biological evaluation. Its synthesis in good overall yield was completed in this laboratory prior to a report by Bendich *et al.*[2] describing an alternate procedure without experimental details. Our route is analogous to the method of Gabriel and Colman[3] for the synthesis of 6-methylpurine. 6-Trifluoromethyl-2-thiouracil[4] was converted to 6-trifluoromethyluracil in a manner patterned after the

(1) Smith Kline & French Laboratories Fellow, 1955–1957.

(2) A. A. Bendich, Giner-Sorolla, and J. J. Fox, *Ciba Foundation Symposium on the Chemistry and Biology of Purines*, Little, Brown & Co., Boston, 1957, p. 3.

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preparation of uracil from thiouracil.[5] This compound was also prepared, in poor yield, from ethyl trifluoroacetoacetate and urea in the presence of sodium ethoxide as reported for similar cases.[6] A nitro group was introduced into the 5-position of 6-trifluoromethyluracil by using a strong nitrating mixture, and the two hydroxyl groups of the nitro compound were replaced by chlorination with phosphorus oxychloride and dimethylaniline. The chlorine atoms were exchanged with amino groups, and the resulting 2,4-diamino-5-nitro-6-trifluoromethylpyrimidine was hydrogenated to 2,4,5-triamino-6-trifluoromethylpyrimidine. The sulfate of this compound underwent purine ring closure when treated with formamide by the general directions of Robins *et al.*[7] 2-Amino-6-trifluoromethylpurine from this sequence was a crystalline amphoteric compound whose infrared spectrum showed pronounced amino (2.84 μ) and imino (2.99 μ) bands. The ultraviolet spectrum was determined in 3*N* hydrochloric acid, where it demonstrated a weak shoulder between 230 and 240 μ, and a maximum at 334 mμ ($\epsilon = 5.05 \times 10^3$); in water to which just sufficient hydrochloric acid was added to accomplish solution (*p*H 2.82), a weak shoulder was observed between 235 and 245 mμ and a maximum at 324 mμ ($\epsilon = 5.88 \times 10^3$).

EXPERIMENTAL

6-Trifluoromethyluracil. Method A. To a solution of 4 g. of sodium ethoxide in 30 ml. of absolute ethanol was added 1.82 g. of urea and 5.5 g. of ethyl trifluoroacetate. The mixture was refluxed for 24 hr., and the solvent was distilled off. The brown residue was dissolved in 15 ml. of water, cooled in an ice bath, and acidified with concentrated hydrochloric acid to produce 1.1 g. (20%) of colorless crystals; m.p. 230–232°. Recrystallization from hot water did not elevate the melting point.

Anal. Calcd. for $C_5H_3F_3N_2O_2$: C, 33.34; H, 1.68. Found: C, 32.70; H, 1.85.

Method B. A mixture of 46 g. of 6-trifluoromethyl-2-thiouracil,[4] 41.4 g. of chloroacetic acid and 500 ml. of water was stirred and refluxed for 4 hr. The resulting pale yellow solution was cooled to room temperature and a colorless crystalline solid precipitated. After addition of 120 ml. of 38% hydrochloric acid the suspension was refluxed and stirred for 6 hr. The solvents were distilled off under reduced pressure and the colorless residue was recrystallized from hot water to yield 38.4 g. (88%) of colorless prisms; m.p. 230–232°. A mixture melting point of this material with a sample obtained by Method A was not depressed. Elementary analysis indicated complete removal of sulfur.

5-Nitro-6-trifluoromethyluracil. A mixture of 30 g. of 6-trifluoromethyluracil, 15 ml. of concentrated sulfuric acid and 60 ml. of fuming nitric acid (d = 1.5) was heated on a steam bath for 1 hr. The yellow solution was transferred to an evaporating dish and heated an additional hour on a steam bath, cooled, and 50 g. of crushed ice was added. The light yellow crystals were recrystallized from a small amount of water to yield 22.2 g. (59%) of almost colorless prisms; m.p. 239–241°. A mixture of this material and 6-trifluoromethyluracil melted at 179–193°. Sodium hydroxide and ferrous hydroxide tests for the nitro group were positive.

Anal. Calcd. for $C_5H_2F_3N_3O_4$: C, 26.68; H, 0.89. Found: C, 26.94; H, 1.20.

2,4-Dichloro-5-nitro-6-trifluoromethylpyrimidine. To 15 g. of 5-nitro-6-trifluoromethyluracil was added 15 ml. of freshly distilled dimethylaniline and 120 ml. of freshly distilled phosphorus oxychloride, while cooling in an ice bath. The dark green solution was refluxed for 2 hr., allowed to stand at room temperature overnight, and concentrated under reduced pressure to one third the original volume. The residual liquid was slowly poured onto 300 g. of stirred crushed ice, the mixture was extracted thoroughly with ether, dried over anhydrous sodium sulfate, and the solvent was distilled off. The resulting black, oily residue was distilled under reduced pressure to yield 9.4 g. (54%) of a light yellow oil; b.p. (0.3 mm.) 48°, which formed a low melting solid when cooled below 0°. A ferrous hydroxide test for the nitro group was positive.

Anal. Calcd. for $C_5Cl_2F_3N_3O_2$: C, 22.92. Found: C, 21.76; 21.70.

2,4-Diamino-5-nitro-6-trifluoromethylpyrimidine. To a saturated solution of ammonia in ethanol (40 ml.), cooled in an ice bath, was added slowly and carefully 8 g. of 2,4-dichloro-5-nitro-6-trifluoromethylpyrimidine. The resulting bright yellow mixture was refluxed for 10 min. and then allowed to stand at room temperature for 24 hr. The precipitated ammonium chloride was filtered and the filtrate was evaporated to dryness on a steam bath. The crystalline residue was suspended in 30 ml. of hot water, cooled, and filtered. Recrystallization from aqueous ethanol afforded 5.4 g. (79%) of bright yellow crystals; m.p. 186–189°. For analysis, a sample was recrystallized from a small amount of ethanol to give bright yellow needles, m.p. 188–190°.

Anal. Calcd. for $C_5H_4F_3N_5O_2$: C, 26.91; H, 1.81. Found: C, 26.62; H, 1.81.

2,4,5-Triamino-6-trifluoromethylpyrimidine. A solution of 4.5 g. of 2,4-diamino-5-nitro-6-trifluoromethylpyrimidine in 100 ml. of absolute ethanol was hydrogenated at 2 atmospheres pressure and room temperature in the presence of 0.2 g. of Adams' catalyst until the hydrogen uptake ceased (20 min.). The catalyst was removed and the brown filtrate was concentrated to dryness under reduced pressure. The residue was recrystallized from about 25 ml. of water, using decolorizing carbon, to afford 3.7 g. (87%) of light tan crystals; m.p. 197–199°.

Anal. Calcd. for $C_5H_6F_3N_5$: C, 31.09; H, 3.13. Found: C, 30.90; H, 3.14.

This material (3.0 g.) was converted to the sulfate by dissolving in 15 ml. of warm 10% sulfuric acid and evaporating the solution to dryness on a steam bath. The light yellow crystalline residue was recrystallized from ethanol-ether, using decolorizing carbon, to give 3.3 g. (88%) of a colorless powder; m.p. 173–175° dec., with preliminary softening at 160°.

Anal. Calcd. for $C_{10}H_{14}N_{10}F_6SO_4$: C, 24.80; H, 2.92. Found: C, 25.05; H, 2.81.

2-Amino-6-trifluoromethylpurine. To 3.0 g. of 2,4,5-triamino-6-trifluoromethylpyrimidine sulfate was added 20 ml. of redistilled formamide. The mixture was heated at 180–190° bath temperature for 20 min., allowed to cool to 30°, diluted with 20 ml. of water, and cooled to 0° for 24 hr. The light tan crystals were filtered, and washed with water, ethanol, and ether. The product (2.0 g., 80%) was precipitated twice with ammonia from hot 10% hydrochloric acid, using decolorizing carbon, to produce colorless crystals; m.p. above 320°.

Anal. Calcd. for $C_6H_4F_3N_5$: C, 35.47; H, 1.99. Found: C, 35.62; H, 2.00.

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Preparation of *p*- and *m*-Aminomethylcyclohexylcarboxylic Acid

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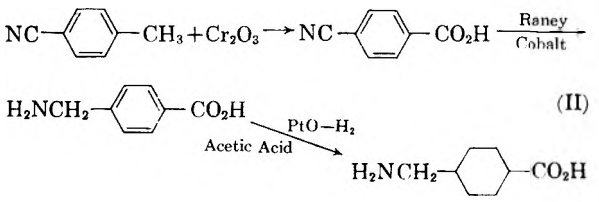
Amino acids containing cycloaliphatic groups have been neglected in the search for fiber-forming polymers although ω-aminocarboxylic acids and their derivatives have received considerable attention. Two cycloaliphatic amino acids, *p*- and *m*-aminomethylcyclohexylcarboxylic acid, were prepared in our laboratory. The meta compound (I) has not previously been reported in the literature; the only preparation of the para compound (II) reported involved a chemical reduction of *p*-aminomethylbenzoic acid prepared from *p*-cyanobenzylchloride.[1] Our three-step synthesis is illustrated in



the accompanying scheme. The starting material may be *m*- or *p*-tolunitrile depending upon the amino acid desired.

The *p*-cyanobenzoic acid prepared from *p*-tolunitrile by chromium trioxide oxidation was first reported by Adkins and Scanley[2] who credited B. F. Aycock with the experimental procedure. Apparently Aycock has not published experimental details; therefore, a procedure for oxidation with chromium trioxide is included. The yields obtained by using this method are higher than those obtained by the Sandmeyer method.

The Albert and Magrath[3] method, using Raney nickel in ammonia, was followed for the reduction of *p*-cyanobenzoic acid. This method resulted in higher yields but the product contained more impurities than when the reduction was carried out using palladium in ammonia. Practically a quantitative yield of (II) (m.p. 238–240°—probably preferential preparation of *cis* isomer) was obtained when the aromatic nucleus was reduced in glacial acetic acid using platinum oxide as catalyst. It is interesting to note that the chemical reduction method[1] for the preparation of (II) produced two forms, an α-form which softened at 270° and a β-form which decomposed between 220–229°.

The *m*-aminomethylcyclohexylcarboxylic acid (I) was prepared from *m*-tolunitrile. A chromic acid oxidation, followed by the reduction of the nitrile group and the aromatic ring gave the new compound (I), melting point 203–204°. Acetyl derivatives of (I) and (II) were prepared and characterized for the first time, and the reduction product of *p*-acetamidomethylbenzoic acid was also prepared.

EXPERIMENTAL

Chromic oxide oxidation of p-tolunitrile. A solution of 35.1 g. (0.3 mole) of *p*-tolunitrile and 570 ml. of glacial acetic acid was placed in a 1-l., three necked flask equipped with a stirrer and a thermometer. Concentrated sulfuric acid, 45 ml., was added slowly to this solution. The reaction flask was cooled to 5° and 90 g. (0.9 mole) of chromic oxide was added in small portions at such a rate that the temperature did not rise above 10°. The reaction materials were stirred at 0–10° for 2 hr., and the temperature was then allowed to rise to 25° during an additional hour. The contents of the reaction flask were poured onto ice, and the solid products were filtered off. The crude material was dissolved in sodium carbonate, and the *p*-cyanobenzoic acid was precipitated with hydrochloric acid. The purification was repeated and the crude acid was recrystallized from water. The product, obtained in 57% yield, melted at 219–220°, in agreement with the value reported by Adkins and Scanley.[3]

Reduction of p-cyanobenzoic acid with Raney Cobalt. A mixture of 14 g. (0.09 mole) of *p*-cyanobenzoic acid, about 2 g. of Raney Cobalt (W-6 or W-7), 40 ml. of 28% aqueous ammonia and 150 ml. of water was shaken in the Parr Hydrogenerator at 25° under a starting hydrogen pressure of 3 atm. The theoretical amount of hydrogen was taken up within 3 hr. After removing the catalyst by filtration, the violet solution was boiled to remove ammonia, and a solid product precipitated. After recrystallization from water, a pink colored product, *p*-aminomethylbenzoic acid, m.p. 347–350° (closed tube), was obtained in 80% yield. This melting point is in agreement with Dewing.[4] Several recrystallizations from water with the aid of carbon black were necessary in order to obtain a white product.

Reduction of p-aminomethylbenzoic acid. *p*-Aminomethylbenzoic acid, 6.12 g. (0.04 mole) was reduced in glacial acetic acid, 100 ml., with 0.2 g. platinum oxide as catalyst. The reduction was carried out in the low pressure Parr Hydrogenerator at 60° and the reaction was completed in 16–24 hr. After filtering the catalyst, the solution was evaporated to dryness. The residue, the acetate of the amino acid, was dissolved in water. Sulfuric acid was added in order to release the acetic acid upon boiling. After the last traces of acetic acid were removed, enough barium hydroxide was added to remove all the sulfate ions as barium sulfate. After evaporating the filtrate to a small volume, the aliphatic amino acid was then obtained on diluting with acetone. Practically a quantitative yield of (II) was obtained, m.p. 237–240°.

Anal. Calcd. for $C_8H_{15}O_2N$: C, 61.14; H, 9.55. Found: C, 60.30; H, 9.36.

Acetylation of p-aminomethylbenzoic acid. The amino acid, 5 g., was heated on a steam cone with 60 cc. of acetic anhydride and 8 drops of sulfuric acid for 0.5 hr. The product, *p*-acetamidomethylbenzoic acid, after standing 2 hr. at 25° was poured onto ice. The solid product, obtained on evaporation of the liquid, was extracted with potassium hydroxide solution and was recrystallized from a large volume of xylene, m.p. 199–120° (compound was not previously reported).

Anal. Neut. equiv.: Calcd. 193. Found: 193.

Reduction of p-acetamidomethylbenzoic acid. Reduction of *p*-acetamidomethylbenzoic acid in acetic acid with platinum oxide gave *p*-acetamidomethylcarboxylic acid.

Anal. Neut. equiv.: Calcd. 199. Found: 198.

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Oxidation of m-tolunitrile. Oxidation of *m*-tolunitrile to *m*-cyanobenzoic acid was carried out with chromium trioxide in a mixture of acetic and sulfuric acids as described above for *p*-tolunitrile. The conversion was 66% and the product, *m*-cyanobenzoic acid, melted at 218-220°. The compound had previously been prepared using the Sandmeyer method,[5] m.p. 217°.

Reduction of m-cyanobenzoic acid with Raney Cobalt. The techniques used in the reduction were similar to those used with the *para* isomer. The product obtained was considerably more soluble than *p*-aminomethylbenzoic acid in water. The melting point was 273–275° (closed tube). This value is not in agreement with the melting point reported by Reinglass[6] (215–218°).

Anal. Calcd. for $C_8H_9O_2N$: C, 63.57; H, 5.96; N, 9.27. Found: C, 63.33; H, 5.42; N, 9.17.

Reduction of m-aminomethylbenzoic acid to m-aminomethylcyclohexylcarboxylic acid. The reduction was carried out in glacial acetic acid using platinum oxide as catalyst. The product (I), not previously reported, melted at 203–204° using the method of isolation reported above for the *para* derivatives.

Anal. Calcd. for $C_8H_{15}O_2N$: C, 61.14; H, 9.55. Found: C, 60.30; H, 9.36.

Acetylation of m-aminomethylbenzoic acid. The acetylation was carried out as previously described using acetic anhydride. The product obtained, not previously reported, melted at 162–164°.

Anal. Neut. equiv.: Calcd. 193. Found: 196.

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Mannich Derivatives of Analgesic Agents

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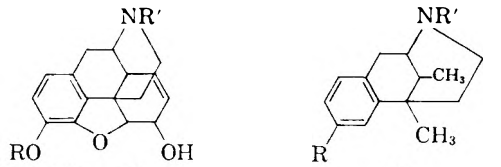
The recent disclosure[1] that replacement of the methyl group on the nitrogen of morphine and meperidine by phenethyl and *p*-aminophenethyl groups, respectively, results in a marked increase in analgesic potency has stimulated renewed interest along these lines.[2–5] In the morphinan[5] series, compounds have emerged with activities some fifty times that of the *N*-methyl parent. Perhaps the most dramatic increase in potency (500 fold) has been that resulting from substitution of 3-oxo-3-phenylpropyl for the methyl radical of ethyl 1-methyl-4-phenylisonipecotate (meperidine).[6] We wish to report an extension of this last-mentioned modification to other series of analgesics.

FIGURE 1



Ia. R = R′ = H
b. R = CH_3, R′ = H
c. R = H, R′ = CH_2CH_2COPh
d. R = CH_3, R′ = CH_2CH_2COPh
e. R = R′ = CH_3

II

IIa. R = R′ = H
b. R = OH, R′ = H
c. R = H, R′ = CH_2CH_2COPh
d. R = OH, R′ = CH_2CH_2COPh
e. R = OH, R′ = CH_3
f. R = OCH_3, R′ = CH_3

The substitution of 3-oxo-3-phenylpropyl for the hydrogen of a secondary amine can usually be achieved by the Mannich reaction using acetophenone and paraformaldehyde. With the bases under consideration, normorphine (Ia), norcodeine (Ib), 5,9-dimethyl-6,7-benzomorphan (IIa), and 2′-hydroxy-5,9-dimethyl-6,7-benzomorphan (IIb), normal procedures[5b,7] failed. Ultimately the desired compounds, Ic, Id, IIc, and IId, were obtained by means of the amine replacement reaction. In this reaction as originally presented by Snyder and Brewster[8] the secondary amine in large excess was heated with a Mannich base or its methiodide; the resulting amine exchange gave the new Mannich base. The reaction has proved useful in preparing Mannich bases of amines which do not undergo the normal condensation.[9] Conditions were modified on finding that equivalent amounts of the secondary amine and Mannich quaternary salts in dimethylformamide reacted at room temperature to give the expected product in good yield. Sodium carbonate was used to bind released acid and nitrogen to agitate the mixture and remove trimethylamine.

In the case of the phenolic compounds (Ia, IIb) the possibility of ring substitution was eliminated by subjecting the presumed Mannich bases (Ic, IId) to the action of base in the presence of methyl iodide. Loss of the 3-oxo-3-phenylpropyl group took place readily and the resultant *N*-methyl analogs were identified as the methiodides.

3-Phenyl-3-oxopropyl-normorphine (Ic) and norcodeine (Id) are from two to three times less potent analgesics in mice than morphine and codeine respectively, while the benzomorphans IIc

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and IId are somewhat more effective than the *N*-methyl counterparts.[10,11]

EXPERIMENTAL

Melting points are uncorrected unless otherwise noted. Microanalyses are by Paula M. Parisius of the Institutes Service Analytical Laboratory, Dr. William C. Alford, director.

5,9-Dimethyl-6,7-benzomorphan (IIa) *picrate.* A solution of 1.7 g. of 2,5,9-trimethyl-6,7-benzomorphan (from 2.2 g. of hydrochloride)[10] in 8 ml. of chloroform was added during 0.7 hr. to a stirred solution of 1.0 g. of cyanogen bromide (Eastman) in 10 ml. of chloroform. The solution was refluxed for 2 hr. and evaporated to dryness *in vacuo*. The residue and 36 ml. of 6% hydrochloric acid were refluxed for 20 hr. Cooling and ammonium hydroxide addition liberated an oil which was dried in ether. Evaporation of the ether left 1.5 g. of base which with 1.5 g. of picric acid and 10 ml. of alcohol (heated to solution), gave on cooling to 25° 1.7 g. (50%) of IIa picrate m.p. 232–233° (dec., corr.).

Anal. Calcd. for $C_{20}H_{22}N_4O_7$: C, 55.81; H, 5.15. Found: C, 55.60; H, 5.16.

The *hydrochloride* crystallized from acetone-ether in long needles, m.p. 171.5–173.5° (corr.). It was dried 0.5 hr. at 139° for analysis.

Anal. Calcd. for $C_{14}H_{20}ClNO$: C, 70.71; H, 8.48. Found: C, 70.39; H, 8.35.

2'-Hydroxy-5,9-dimethyl-6,7-benzomorphan (IIb). Two g. of 2'-hydroxy-2,5,9-trimethyl-6,7-benzomorphan[10] and 4 ml. of acetic anhydride were kept at 95–100° for 0.5 hr., cooled, diluted with ice water, and after 5 min. made alkaline with aqueous potassium hydroxide while keeping ice cold. The oil was quickly shaken into ether. Drying and evaporation of the ether left 2.3 g. of ester which was subjected to *N*-demethylation (1 g. of cyanogen bromide) as described above, except that chloroform or 2:1 benzene butanol was used to extract the crude IIb which weighed 1.8 g. It crystallized from 5 ml. of acetone in a yield of 1.1 g. (60%); m.p. 225–231°, and 232–235° (corr.) after two recrystallizations from methanol.

Anal. Calcd. for $C_{14}H_{19}NO$: C, 77.38; H, 8.81. Found: C, 77.20; H, 8.86.

The *hydrochloride*, small prisms from absolute ethanol-ether, melted at 291–294° (dec., corr.).

Anal. Calcd. for $C_{14}H_{20}ClNO$: C, 66.25; H, 7.94. Found: C, 66.14; H, 8.13.

N-(3-Oxo-3-phenylpropyl)normorphine (Ic). Normorphine[12] (Ia, 10 g.), 12 g. (1.1 equivalent) of β-dimethylaminopropiophenone methiodide, 3.6 g. (2 equivalents) of sodium carbonate, and 50 ml. of dimethylformamide were agitated with a slow stream of nitrogen which also removed trimethylamine. After 4 hr. addition of water gave an oil which readily crystallized. Filtration and washing with water, then alcohol gave 11.2 g. of Ic which melted at 179–182°. Recrystallization from alcohol yielded 10.0 g. (74%), m.p. 180–183°.

Anal. Calcd. for $C_{25}H_{25}NO_4$: C, 74.42; H, 6.25. Found: C, 74.13; H, 6.20.

The Ic, alcoholic sodium hydroxide, and excess methyl iodide were left overnight. The recovered crude product was put in acetone suspension with methyl iodide. The resultant methiodide gave no depression in melting point on admixture with codeine methiodide.

N-(3-Oxo-3-phenylpropyl)norcodeine (Id) *hydrochloride.* This compound was prepared from norcodeine (Ib)[12] as described above. The hydrochloride of Id crystallized from water as the dihydrate, m.p. 168–171°.

Anal. Calcd. for $C_{26}H_{28}ClNO_4.2H_2O$: H_2O, 7.3. Wt. loss (100°), 7.2. For the anhydrous hydrochloride: C, 68.79; H, 6.22. Found: C, 68.80; H, 6.13.

2-(3-Oxo-3-phenylpropyl)-5,9-dimethyl-6,7-benzomorphan (IIc) *hydrochloride.* As described in the synthesis of Ic, the yield of IIc from IIa was 70%. The hydrochloride salt was purified from alcohol; m.p. 181–183°.

Anal. Calcd. for $C_{23}H_{28}ClNO$: C, 74.67; H, 7.63. Found: C, 74.35; H, 7.78.

2'-Hydroxy-5,9-dimethyl-2-(3-oxo-3-phenylpropyl)-6,7-benzomorphan (IId). This compound prepared in 85% yield as described above was freed of a little iodide with dilute aqueous sodium hydroxide. Recrystallized from alcohol, it melted at 175–176°.

Anal. Calcd. for $C_{23}H_{27}NO_2$: C, 79.05; H, 7.79. Found: C, 78.71; H, 7.89.

2'-Methoxy-2,5,9-trimethyl-6,7-benzomorphan (IIf) *methiodide.* Alcoholic sodium hydroxide, IIe[10] and methyl iodide gave after 1 hr. at 25° crystals which were collected and purified from alcohol; m.p. 173–178°.

Anal. Calcd. for $C_{17}H_{26}INO$: C, 52.71; H, 6.77. Found: C, 52.78; H, 6.98.

Similar treatment of IId gave the same compound, m.p. 170–177°, after purification from alcohol. The melting point was not lowered on admixture with the above sample and the infrared spectra were identical.

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(10) E. L. May and E. M. Fry, *J. Org. Chem.*, 22, 1366 (1957).

(11) Personal communication from Dr. N. B. Eddy, Chief, Section on Analgesics.

(12) Supplied by Merck & Co. Inc., Rahway, N. J.

Indoxyl Acetate from Indole

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Received July 29, 1958

The observation of Barrnett and Seligman,[1] later extended by others,[2–4] that indoxyl acetate was suitable for the detection of acetylcholinesterase in tissue slices suggested to us that this technique could be adapted to the determination of this enzyme in serum. In the course of our investigations for a method of synthesizing substituted indoxyl acetates that would lend themselves to a colorimetric procedure for the determination of the activity of the enzyme, a new method of preparation of indoxyl acetate was found. Oxidation of indole with various reagents has been reported to give indoxyl[5] but the yields are not good. Halogenated indoles are reported to be inert to alkaline hydrolysis.[6] The usual greater reactivity of iodine compounds compared to that of other halogen compounds, cou-

(1) R. J. Barrnett and A. M. Seligman, *Science*, 114, 579 (1951).

(2) R. J. Barrnett, *Ant. Record*, 114, 577 (1952).

(3) S. J. Holt and R. F. J. Withers, *Nature*, 170, 1012 (1952).

(4) S. J. Holt and R. F. J. Withers, *J. Physiol. (London)*, 119, 36P (1953).

(5) O. Baudische and A. B. Hoschek, *Ber.*, 49, 2580 (1916).

(6) O. Mingoia, *Gazz. chim. ital.*, 60, 509 (1930).

pled with the observation of Weissgerber[7] that iodine was removed by dilute hydrochloric acid with the production of oxindole, led us to attempt the reaction of 3-iodoindole with silver acetate under mild acidic conditions. We find that in acetic acid solution at room temperature over extended periods of time indoxyl acetate is produced in fair yields. This novel preparation of this class of compounds is expected to open the way to derivatives unobtainable by other routes.

EXPERIMENTAL

3-Iodoindole. A solution of 11.7 g. of indole (0.1 mole) and 4.0 g. (0.1 mole) of sodium hydroxide in 400 ml. of methanol was treated with 101 ml. of iodine–potassium iodide solution containing 25.4 g. (0.2 mole) of iodine with vigorous stirring. No heat was evolved and it was found that the iodine solution could be added as rapidly as possible. Water was added with stirring and the precipitate was filtered and washed with water. This material is unstable and should be used immediately without purification.

Indoxyl acetate. The crude iodoindole was dissolved in 400 ml. of glacial acetic acid and 33.4 g. (0.2 mole) of silver acetate was added in one portion and the suspension was stirred for 20 hr. At the end of this period the mixture was filtered and the filtrate was evaporated to dryness under vacuum. The dark purple residue was recrystallized twice from a 40% solution of methanol in water. The product crystallized as fine white needles which melted at 126° (reported 126–127°).[1] A mixed melting point with an authentic sample of indoxyl acetate was not depressed. The overall yield was 5.4 g. or 28%.

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(7) R. Weissgerber, *Ber.*, **46**, 655 (1913).

Reaction of Carbon Suboxide with Nitro Alcohols

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In view of the reactions of carbon suboxide (I) with alcohols,[2] amines, acids and related classes of compounds,[3] it was anticipated that I would also react with primary and secondary nitroparaffins to yield α,α'-dinitro diketones. Since α-nitro ketones possessing alpha hydrogen are unstable compounds, secondary nitro- and *gem*-dinitro compounds were chosen, so that the resulting products would not contain an alpha hydrogen. When 2-nitropropane or 1,1-dinitroethane was treated at room temperature with an ethereal solution of I in the absence of a catalyst or in the presence of such catalysts as sulfuric acid and triethylamine, no addition took place, and the nitro compounds were recovered unchanged. The sulfuric acid caused polymerization of I[2] and the triethylamine formed an addition compound with I which is probably similar to those resulting from the reaction of alkaloids and I.[4]

Since I did not react with nitroparaffins, reactions were initiated with primary, secondary, and tertiary 2-nitroalcohols in order to establish whether the presence of a nitro group adjacent to the reaction center would affect the esterification. It was found that the expected malonic esters formed readily at room temperature, but in small yields unless a catalyst was present. Thus the reaction of 2-nitro-2-methyl-1-propanol (II) with excess of I in ether at room temperature for 24 hours gave di(2-methyl-2-nitropropyl)malonate (III) in only a 39% yield. The yield of III increased to 53% in the presence of sulfuric acid, which, however, also caused extensive polymerization of I. This polymerization was minimized when the reaction was carried out in the presence of hydrogen chloride or aluminum chloride, affording III in yields of 87% and 100%, respectively.

The structure of ester III was established by elemental analysis, and by a mixed melting point determination with an authentic sample of III which was prepared from malonic acid and II and which in its turn analyzed correctly.

Besides compound II, 3-methyl-3-nitro-2-butanol, 2-nitro-1-butanol and 2-nitroethanol (IV) reacted smoothly with I. The ester (V) which was obtained with IV was an oil which could not be distilled even in high vacuum without causing decomposition. However, the structure of V was confirmed by the identity of its infrared spectrum with that of the ester, prepared from IV and malonic acid.

The reaction of I with 2,2-dinitropropanediol yielded a polymeric material.

$$HOCH_2—C(NO_2)_2—CH_2OH + C_3O_2 \xrightarrow{AlCl_3}$$

$$\left[\begin{array}{l} O \\ \| \\ -C-CH_2—CO_2—CH_2—C(NO_2)_2—CH_2—O- \end{array}\right]_n$$

VI

It was soluble in hot methanol, and on addition of water was partially converted to a solid, the elemental analysis of which was in agreement with the unit structure of polyester VI. The remainder was an oil which could not be solidified.

EXPERIMENTAL

The carbon suboxide was produced by thermal degradation of diacetyltartaric anhydride. Essentially the method of Hurd and Pilgrim[5] was followed, with one variation. The

(1) From the M.S. dissertation of Robert Miller, Purdue University, May, 1956.

(2) G. Hagelloch and E. Feess, *Ber.*, **84**, 730 (1951).

(3) L. H. Reyerson and Kenneth Kobe, *Chem. Revs.*, **7**, 479 (1930).

(4) O. Diels and K. Hansen, *Ber.*, **59**, 2555 (1926).

(5) C. D. Hurd and F. D. Pilgrim, *J. Am. Chem. Soc.*, **55**, 757 (1933).

procedure requires that the fused anhydride at 150° be forced by displacement with mercury into a tube kept at 675°. A safer and more convenient method consisted of using sand instead of mercury.

Di(2-methyl-2-nitropropyl)malonate. (a) With carbon suboxide. To a Dry Ice trap, containing 35.7 g. (0.30 mole) of 2-nitro-2-methyl-1-propanol dissolved in 120 ml. of anhydrous ethyl ether and 0.5 g. of anhydrous aluminum chloride at −78°, was distilled 20 g. (0.29 mole) of carbon suboxide. The trap was then provided with a Dry Ice condenser and drying tube, and the reaction mixture was allowed to warm up to 25° and remain at that temperature for 24 hr. The solvent was then evaporated, the residue taken up in hot methanol and after filtration, small portions of water were added until no more material precipitated. The mixture was then filtered, yielding 45.9 g. (100%) of di(2-methyl-2-nitropropyl)malonate, m.p. 50–51° after recrystallization from hexane.

Anal. Calcd. for $C_{11}H_{18}N_2O_8$: C, 43.13; H, 5.88; N, 9.15. Found: C, 42.99; H, 5.98; N, 9.31.

(*b*) *With malonic acid.* To a flask equipped with a condenser were added 10.4 g. (0.1 mole) of malonic acid, 25.0 g. (0.21 mole) of 2-nitro-2-methyl-1-propanol, 85 ml. of ethylene chloride, and 4 ml. of conc. sulfuric acid. The mixture was refluxed for 30 hr. and the lower ethylene chloride layer was washed with water and a sodium bicarbonate solution. The solvent was removed *in vacuo*, the residue taken up in methanol, and reprecipitated by the addition of water. This gave a 35% yield of ester, m.p. 50–51° after recrystallization from hexane. A mixed melting point determination with the ester obtained from the procedure (*a*) showed no depression.

The following esters were prepared by procedure (a).

2-Di(3-methyl-3-nitrobutyl)malonate, m.p. 83–84° after recrystallization from hexane and then absolute ethanol (yield 85%).

Anal. Calcd. for $C_{15}H_{22}N_2O_8$: C, 46.70; H, 6.63; N, 8.38. Found: C, 46.69; H, 6.76; N, 8.44.

Di(2-nitrobutyl)malonate, $n_D^{19.5}$ 1.4587, was distilled at 1 micron at a bath temperature of 57° (yield 80%).

Anal. Calcd. for $C_{11}H_{18}N_2O_8$: C, 43.13; H, 5.88; N, 9.15. Found: C, 43.22; H, 5.81; N, 9.27.

Di(2-nitroethyl)malonate, $n_D^{19.5}$ 1.4670, decomposed on distillation at 5 microns at a bath temperature of 45°.

Preparation of a polyester (VI) *from carbon suboxide and 2,2-dinitropropanediol.* 2,2-Dinitropropanediol[6] (32.2 g., 0.2 mole), 0.5 g. of anhydrous aluminum chloride and 25 g. (0.37 mole) of carbon suboxide in ether were allowed to react as described in procedure (a). On cooling the reaction mixture, 0.52 g. of a solid, m.p. 95–110° precipitated. On evaporating the solvent from the filtrate, an oil remained which was taken up in hot methanol; after addition of water, 6.4 g. of solid precipitated. Evaporation of the filtrate left 32 g. of an oil which could not be crystallized. It solidified to a waxy solid on cooling, but melted before reaching room temperature. The above solid melted at 82–83° after recrystallization from absolute ethanol and analyzed correctly for VI.

Anal. Calcd. for $C_6H_6N_2O_8$: C, 30.78; H, 2.58; N, 11.97. Found: C, 31.06; H, 2.89; N, 11.99.

When the above diol and malonyl dichloride were refluxed[7] in dioxan for 23 hr., a polymer was obtained which softened at 115–123° but gave the same analysis as the polyester VI.

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(6) H. Feuer, G. B. Bachman, and J. P. Kispersky, *J. Am. Chem. Soc.*, **73**, 1360 (1951).

(7) Unpublished results from the Ph.D. thesis of J. P. Kispersky, Purdue University, August 1950.

Preparation of 3-Triethoxysilylpropylamine and 1,3-Bis(3-aminopropyl)tetramethyldisiloxane

John C. Saam and John L. Speier

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Primary and secondary amines with silicon hydrides in the presence of chloroplatinic acid form hydrogen and unidentified products, presumably aminosilanes.[1] With allylamine triethoxysilane and chloroplatinic acid led to complex products along with hydrogen. However, despite the presence of an amino hydrogen, allylaminotrimethylsilane (I) reacted with triethoxysilane in the presence of chloroplatinic acid to give a small amount of tetraethoxysilane and silane with a product assumed to be 3-triethoxysilylpropylaminotrimethylsilane. *sym*-Tetramethyldisiloxane and I presumably gave 1,3-bis(3-trimethylsilylaminopropyl)tetramethyldisiloxane. These adducts were not isolated, but ethanol converted them in good yield to the free amines II and III, which were isolated and identified.

$CH_2{=}CH{-}CH_2NHSi(CH_3)_3$
I

$(C_2H_5O)_3SiCH_2CH_2CH_2NH_2$
II

$[NH_2CH_2CH_2CH_2Si(CH_3)_2]_2O$
III

$C_2H_5O(CH_3)_2SiCH_2CH_2CH_2Cl$
IV

$C_2H_5O(CH_3)_2SiCH_2CH_2CH_2NH_2$
V

The physical properties of II differed slightly from those previously reported,[2] but the infrared spectrum was identical with that of an authentic sample. The structure of III was established by an independent synthesis. The reaction of 3-chloropropyldimethylethoxysilane (IV) with liquid ammonia formed 3-ethoxydimethylsilylpropylamine (V). The hydrolyzate from V had the same infrared spectrum and yielded the same dihydrochloride as that of III.

EXPERIMENTAL

Allylaminotrimethylsilane was prepared in 70% yield.[3] Boiling point 111–112°, n_D^{25} 1.4130, d_4^{25} 7675.

3-Triethoxysilylpropylamine (II). A mixture of 115 g. of triethoxysilane, 94.5 g. of allylaminotrimethylsilane and

(1) Unpublished results of this laboratory.

(2) V. B. Jex and D. L. Bailey, French Patent **1,140,301** (1957).

(3) J. L. Speier, R. Zimmerman, and J. Webster, *J. Am. Chem. Soc.*, **78**, 2280 (1956).

0.25 ml. of 0.2 molar chloroplatinic acid in ethanol was refluxed for 4 hr. A slow stream of an inflammable gas presumed to be silane was observed. Absolute ethanol (50 ml.) was then added, and the mixture was distilled to give 26.7 g. of tetraethoxysilane, b.p. 80–90° at 29 mm., n_D^{25} 1.3850, and 94 g. of II (61% yield), b.p. 119–122° at 29 mm., n_D^{25} 1.4220, D_4^{25} 0.9477, R_D calcd. 0.2670, R_D found 0.2676. Jex and Bailey[2] reported b.p. 123° at 30 mm., n_D^{25} 1.4195, D^{25} 0.942.

Anal. Calcd. for $C_9H_{23}NO_3Si$: Si, 12.61; neut. equiv. 221. Found: Si, 12.39; neut. equiv. 221.

1,3-Bis(3-aminopropyl)tetramethyldisiloxane (III). *sym*-Tetramethyldisiloxane (134 g.) was added slowly to refluxing allylaminotrimethylsilane (294 g.) which contained 0.2 ml. of 0.22 molar chloroplatidic acid in ethanol. After the reaction was initiated, the temperature of the mixture was maintained at 110° to 125° by regulating the rate of addition of the siloxane. After the reaction was complete, 100 ml. of absolute ethanol was added and the lower boiling components were distilled from the mixture. The residue was distilled at reduced pressure to give 191 g. (78% yield) of III, b.p. 96–104° at 2.5 mm., b.p. 134–142° at 11.5 mm., n_D^{25} 1.4475–1.4485, D_4^{25} 0.8956–0.8971. R_D calcd. 0.2995, R_D found 0.2989–0.2987.

Anal. Calcd. for $C_{10}H_{28}ON_2Si_2$: Si, 22.60; neut. equiv., 124. Found: Si, 22.38; neut. equiv., 124.5.

A solution of 4.5 g. of III in 200 ml. of anhydrous ether was saturated with dry hydrogen chloride to form the dihydrochloride. Recrystallized twice from ethyl acetate, 1,3-bis(3-aminopropyl)tetramethyldisiloxane dihydrochloride had a m.p. of 250–253°.

Anal. Calcd. for $C_{10}H_{30}ON_2Cl_2Si_2$: Si, 17.45. Found: Si, 17.69.

3-Chloropropyldimethylethoxysilane (IV). To a stirred solution of 252 g. of 3-chloropropyldimethylchlorosilane in 750 ml. of hexane was added 138 g. of absolute ethanol through a tube extending beneath the surface of the liquid. The mixture was refluxed for 2.5 hr., saturated with anhydrous ammonia, and filtered. The precipitate was washed with hexane, and the solvent was removed from the combined filtrates by distillation. The residue was distilled at reduced pressure to give 188.1 g. (69%) of IV. Boiling point 87° at 30 mm., n_D^{25} 1.4270, D_4^{25} 0.9319, R_D calcd. 0.2759, found 0.2755.

Anal. Calcd. for $C_7H_{17}OClSi$: Si, 15.50. Found: Si, 15.54.

3-(Ethoxydimethylsilyl)propylamine (V). A mixture of 90 g. of 3-chloropropyldimethylethoxysilane (IV) and 204 g. of anhydrous ammonia was heated at 95° for 2 hr. in a 1-l. stainless steel bomb. After the bomb was cooled the organic layer was separated from the ammonia-ammonium chloride layer; and a 52.5 g. portion of the product was distilled at reduced pressure to give 25.7 g. of 3-ethoxydimethylsilylpropylamine. Boiling point 79–78° at 24 mm., n_D^{25} 1.4276, D_4^{25} 0.8570. R_D calcd. 0.3004, found R_D 0.2999.

Anal. Calcd. for $C_7H_{19}ONSi$: Si, 17.39; neut. equiv., 161. Found: Si, 17.17; neut. equiv., 160.2.

A mixture of 16 g. of 3-ethoxydimethylsilylpropylamine, 20 ml. of water and 5 g. of potassium hydroxide was extracted with two 20-ml. portions of ether. The ether solution was dried over potassium hydroxide. A 10-ml. portion saturated with dry hydrogen chloride gave 4.15 g. of 1,3-bis(3-aminopropyl)tetramethyldisiloxane dihydrochloride, m.p. 249.5–251.5° from ethanol–ethyl acetate.

Anal. Calcd. for $C_{10}H_{30}ON_2Cl_2Si_2$: Si, 17.45. Found: Si, 17.39.

The remainder of the ether solution was evaporated to yield 10 g. of 1,3-bis(3-aminopropyl)tetramethyldisiloxane, n_D^{25} 1.4480, D_4^{25} 0.8960, R_D calcd. 0.2995, R_D found 0.2988.

Anal. Calcd. for $C_{10}H_{28}ON_2Si_2$: neut. equiv. 124. Found: neut. equiv. 124.6.

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2,5-Dibenzylidene-3-cyclopentenone

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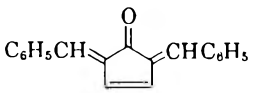
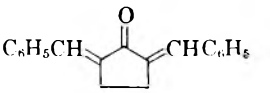
In an investigation of the photochemical properties of 2,5-dibenzylidene-3-cyclopentenone (I), we have encountered unambiguous evidence that I as previously prepared[1] is contaminated with 2,5-dibenzylidenecyclopentanone (II). This impurity was not removed by repeated recrystallization from a variety of solvents. Furthermore, the mixture of I and II gave satisfactory carbon, hydrogen analyses for I. General interest in the unique structure of 2,5-dibenzylidene-3-cyclopentenone has prompted us to relate this evidence together with a



I



II

novel procedure for the elimination of the contaminant.

The unexpected presence of II was first detected in an attempt to prepare the uranyl chloride complex of I. Treatment of a hot, saturated solution of supposedly pure I[2] with uranyl chloride gave in low yield an orange-red, crystalline complex. This complex had an infrared spectrum identical to that of an authentic sample of the uranyl chloride-2,5-dibenzylidenecyclopentanone complex.[3] The complex on dissolution in ethanol precipitated a yellow ketone which was shown by mixed melting point and infrared and ultraviolet spectral identity to be 2,5-dibenzylidenecyclopentanone thus confirming the identity of the contaminant. Cooling of the filtrate, after removal of the highly insoluble complex, gave I, m.p. 156–157° (reported previously,[1] m.p. 150°). A second treatment of I with uranyl chloride gave no complex, and the 2,5-dibenzylidene-3-cyclopentenone recovered had melting point, infrared and ultraviolet absorption identical to those of I after a single treatment with uranyl chloride. 2,5-Dibenzylidene-3-cyclopentenone thus purified showed λ_{max}^{EtOH} 316 mμ (38,900) and 232–234 mμ (11,700).

The failure of I to form a uranyl chloride complex strongly supports the geometric configuration suggested for I by Wanzlick.[1] The structure of the uranyl chloride-2,5-dibenzylidene cycloalkanone complexes will be discussed in a forthcoming report of their photochemical transformations.

EXPERIMENTAL

2,5-Dibenzylidene-3-cyclopentenone (I) (*after Wanzlick*[1]). A solution of 2,5-dibenzylidenecyclopentanone (26 g., 0.1 mole)

(1) H. Wanzlick, *Chem. Ber.*, **86**, 41 (1953).

(2) This material (m.p. 150°) had been recrystallized seven times from trichloroethylene.

(3) P. Pretorius and F. Korn, *Ber.*, **43**, 2744 (1910).

and *N*-bromosuccinimide (19.6 g., 0.11 mole) in 450 ml. of carbon tetrachloride was stirred and irradiated with a General Electric RS sunlamp for 2 hr. During this time, hydrogen bromide was evolved, and by the end of this period the solution had developed a dull red color. The succinimide was removed by filtration. The filtrate was evaporated to a pasty residue. Recrystallization of the residue from trichloroethylene gave greenish-yellow crystals, m.p. 150°, yield (13 g., 50%). Additional recrystallization of this material from trichloroethylene, benzene, xylene, or acetic acid–acetone (1:1) did not alter the melting point.

Purification of 2,5-dibenzylidene-3-cyclopentenone (I). The product I (14.7 g., 0.093 mole, m.p. 150°) described above was dissolved in the least possible volume of hot acetic acid–acetone (1:1). Uranyl acetate dihydrate (10 g.) dissolved in 3.8 ml. of hydrochloric acid was added to the hot solution. An orange-red precipitate began to form immediately. The solution was protected from light with aluminum foil and kept hot for 2 hr. The precipitated complex was filtered from the hot solution. This gave orange-red crystals (4.3 g., 5%) which did not melt below 300° and which showed infrared maxima identical to those of an authentic sample of the uranyl chloride-2,5-dibenzylidenecyclopentanone complex[3] (both spectra were taken in potassium bromide). Cooling of the filtrate gave greenish-yellow plates, m.p. 156–157°. This material gave, after two recrystallizations from trichloroethylene, 9 g. of I, m.p. 156–157°, λ_{max}^{EtOH} 316 mμ (38,900) and 232–234 mμ (11,700).

Anal. Calcd. for $C_{19}H_{14}O$: C, 88.34; H, 5.45. Found: C, 88.12; H, 5.57.

2,5-Dibenzylidene-3-cyclopentenone thus purified did not give a precipitate on further treatment with uranyl chloride, and the material recovered from this second treatment had the same melting point, infrared spectrum, and ultraviolet spectrum as I purified by a single treatment with uranyl chloride.

Recovery of 2,5-dibenzylidenecyclopentanone from the uranyl chloride complex. The complex obtained above was washed with benzene to remove any organic material which had coprecipitated with it, and then warmed in ethanol with stirring until all of the orange-red complex had disappeared. During this process, a yellow precipitate formed which was collected by filtration and recrystallized from benzene giving bright yellow needles, m.p. 182–186° (authentic 2,5-dibenzylidenecyclopentanone m.p. 188–190°), mixed melting point with 2,5-dibenzylidenecyclopentanone 185–190°. This material had infrared and ultraviolet absorption spectra identical to those of authentic 2,5-dibenzylidenecyclopentanone.

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Synthesis of 7-Methyl Steroid Hormones. II. 7β-Methylcortisone Acetate and 7β-Methylhydrocortisone Acetate

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While a considerable number of alkylated steroid hormones have been described in recent years[1] no 7-alkylated cortisone derivatives have been prepared, and we therefore felt that the synthesis of these compounds would be of interest.

The effect on cortical activity associated with the substitution of methyl groups, or halogen (particularly fluorine) atoms, in place of hydrogen in the A, B, and C rings has been reviewed recently,[2] and may be summarized as follows.

If the methyl group or halogen atom is in an α-axial or α-equatorial configuration (2α-,[3] 6α-,[4] 9α-,[5] 12α-[6]) then retention or enhancement of physiological activity is observed.[7]

The paucity of β-axial and β-equatorial substituted corticoids prevents any generalization. The 6β-methyl- and halo-corticoids have been described, and it is established that these are less active than the parent compounds.[2] The only other case of a β-axial methyl substituted hormone is 8β,14α-dimethyl-18-nortestosterone[8] which is inactive as an androgen.

The 7β-methyl compounds described in this work provide the first example of *β-equatorial* substitution by methyl in corticoids[9] and it is therefore interesting to note that activity is lowered by such substitution.

An obvious starting point for the synthesis was the 3,20-bisethylene ketal of 7-ketocortisone acetate (II). Attempts to prepare (II) by *tert*-butyl chromate oxidation of the 3,20-bisethylene ketal (I)[10] led, in poor yield, to a substance showing an

(1) See Part I (C. H. Robinson, Olga Gnoj, W. Charney, M. L. Gilmore, and E. P. Oliveto, *J. Am. Chem. Soc.*, in press) for pertinent references.

(2) J. A. Hogg, 6th National Medicinal Chemistry Symposium of the American Chemical Society, Madison, Wis., June 23–25, 1958.

(3) J. A. Hogg, F. H. Lincoln, R. W. Jackson, and W. P. Schneider, *J. Am. Chem. Soc.*, **77**, 6401 (1955).

(4) G. B. Spero, J. L. Thompson, B. J. Magerlein, A. R. Hanze, H. C. Murray, O. K. Sebek, and J. A. Hogg, *J. Am. Chem. Soc.*, **78**, 6213 (1956). See also G. B. Spero, J. L. Thompson, F. H. Lincoln, W. P. Schneider, and J. A. Hogg, *J. Am. Chem. Soc.*, **79**, 1515 (1957).

(5) J. Fried and E. Sabo, *J. Am. Chem. Soc.*, **79**, 1130 (1957).

(6) D. Taub, R. D. Hofsommer, and N. L. Wendler, *J. Am. Chem. Soc.*, **79**, 452 (1957).

(7) In apparent contradiction to this generalization, 11α-methylhydrocortisone acetate [G. S. Fonken and J. A. Hogg, *Tetrahedron*, **2**, 367 (1958)] is less active than the parent hydrocortisone acetate. However, the methyl group here has been introduced at the carbon bearing the 11β-hydroxyl group, and so the substitution differs from the others described which are α-, or vinylogously α-, to oxygen atoms at C-3 or C-11.

(8) P. Crabbé, G. Ourisson, and T. Takahashi, *Tetrahedron*, in press. J. F. Biellman, P. Crabbé, and G. Ourisson, *Tetrahedron*, in press.

(9) A patent has now appeared [J. C. Babcock and J. A. Campbell, U. S. Patent **2,838,534** (1958)] which outlines the preparation of 7-methyl cortical hormones. However, 7-methylcortisone and hydrocortisone are partially or not at all characterized, and no stereochemistry is assigned.

(10) See, for example, P. N. Rao and P. Kurath, *J. Am. Chem. Soc.*, **78**, 5660 (1956) and C. W. Marshall, R. E. Ray, I. Laos, and B. Riegel, *J. Am. Chem. Soc.*, **79**, 6308 (1957).

ultraviolet absorption maximum at 240 mμ. This material did not give a positive tetrazolium test, but gave a strong positive Zimmermann reaction. (Under the same conditions, the Δ^5-7-ketone grouping gave a weak Zimmermann reaction.) The infrared spectrum indicated the presence of an α,β-unsaturated ketone grouping, C-11 and C-17 carbonyl groups, and an ethylene ketal. Treatment of this substance with alkali produced a chromophore, λ_{max} 313 mμ, suggesting that a 3-substituted-$\Delta^{3,5}$-7-ketone system had been generated.[11] It seems reasonable to suppose that the substance in question is the 3-ethylene ketal of 5-androstene-3,7,11,17-tetrone.

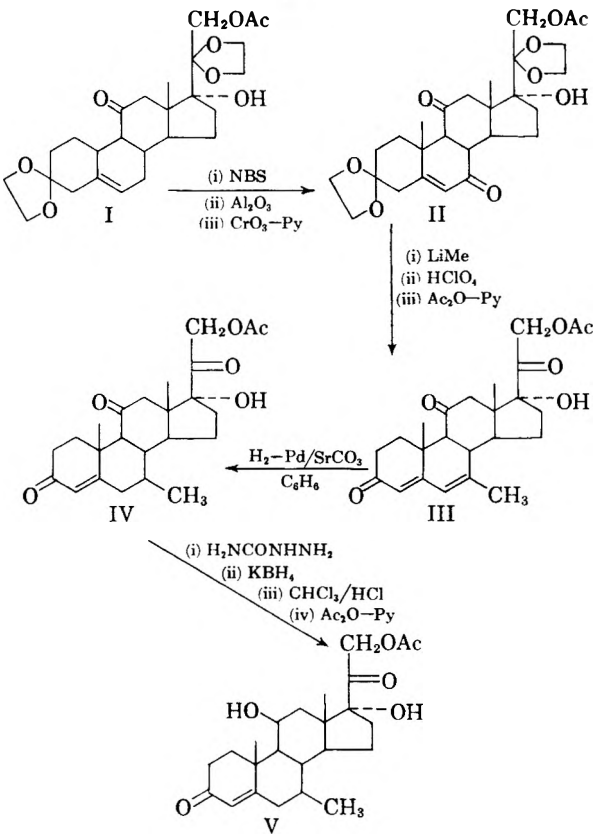
Attempts to oxidize the 3,20-bisketal (I) at C-7 with manganese dioxide[12] proved fruitless, while *N*-bromosuccinimide bromination followed by treatment with silver dichromate[13] led to oils showing ultraviolet absorption maxima at *ca.* 280 mμ, presumably due to formation of the $\Delta^{4,6}$-dien-3-one system.

The 7-ketobisketal (II) was best prepared from (I) in 37% overall yield, by successive Zeigler bromination, treatment with alumina, and chromic acid-pyridine oxidation.[11,14]

When the 7-ketone (II) was treated with lithium methyl in tetrahydrofuran ether, the crude product showed absorption maxima at 243 and 293 mμ. It was observed that heat or acid treatment led to disappearance of the 243 mμ band, with concomitant enhancement of the 293 mμ absorption. This suggests that during work-up the 3-ketal grouping had been lost, and that the crude product contained both the 3-keto-Δ^5-7-hydroxy-7-methyl and the 3-keto-$\Delta^{4,6}$-7-methyl systems. Indeed, treatment of the crude material described above with perchloric acid in methanol at room temperature gave a product which now showed a single ultraviolet maximum at 293 mμ. Regeneration of the 20-ketone had also occurred, as evidenced by the strong positive tetrazolium reaction. Acetylation at C-21 followed by chromatography gave 7-methyl-4,6-pregnadiene-17α,21-diol-3,11,20-trione 21-acetate (III), the ultraviolet (λ_{max} 293 mμ, ϵ 25,000) and infrared spectra (4,6-dien one system, 11-ketone and cortical side chain present) being in accord with the proposed structure.

Hydrogenation of the dienone (III) in benzene solution with palladium-strontium carbonate catalyst[15] until one mole of hydrogen was absorbed, gave 7β-methylcortisone acetate (IV). The configuration at C(7) is assigned on the basis of hydrogenation from the α-face.[16]

Conversion of 7β-methylcortisone acetate (IV) to the hydrocortisone derivative (V) was achieved by potassium borohydride reduction[17] of the 3,20-bissemicarbazone followed by regeneration of the carbonyl groups at C-3 and C-20, using a two phase chloroform aqueous hydrochloric acid procedure,[18] and finally reacetylation at C-21.



EXPERIMENTAL[19]

5-Pregnene-17α,21-diol-3,7,11,20-tetrone 21-acetate 3,20-bisethylene ketal (II). A solution of cortisone acetate bisethylene ketal (I, 5.5 g.) in carbon tetrachloride (300 ml.) and petroleum ether (50 ml.) together with potassium carbonate (1.1 g.) and *N*-bromosuccinimide (2.56 g.) was refluxed, with irradiation, for 4 min., using a 500-watt photoflood lamp (RFL-2, General Electric Co.). The mixture was cooled and filtered, and the filtrate was stirred with alumina (44 g. ethyl acetate–washed) for 2.5 hr., and filtered. Acetone (300 ml.) was then added and the mixture

(11) R. H. Lenhard and S. Bernstein, *J. Am. Chem. Soc.*, **78**, 989 (1956).

(12) P. Meunier, G. Zwingelstein, and J. Jouanneteau, *Bull. soc. chim. biol.*, **35**, 495 (1953).

(13) R. B. Turner, V. R. Mattox, L. L. Engel, B. F. McKenzie, and E. C. Kendall, *J. Biol. Chem.*, **166**, 345 (1946).

(14) H. J. Ringold, G. Rosenkranz, and C. Djerassi, *J. Am. Chem. Soc.*, **74**, 331 (1952).

(15) R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. McLamore, *J. Am. Chem. Soc.*, **74**, 4223 (1952).

(16) L. F. Fieser, *Experientia*, **6**, 312 (1950).

(17) E. P. Oliveto, R. Rausser, L. Weber, E. L. Shapiro, D. Gould, and E. B. Hershberg, *J. Am. Chem. Soc.*, **78**, 1736 (1956).

(18) J. T. Day, U. S. Patent 2,781,367 (1957).

(19) Melting points were obtained on the Kofler block unless otherwise stated. Rotations were measured at 25° in dioxan solution, and at about 1% concentration. We are indebted to the Physical Chemistry Department, Schering Corp., for measurement of ultraviolet and infrared spectra, and rotations. Microanalyses were performed by Mr. Connor (Microanalytical Laboratory, Woodside, Long Island, N. Y.)

stirred overnight, then filtered. The filtrates were evaporated to dryness, and oxidized with a large excess of chromium trioxide–pyridine reagent at 25° overnight. Crystallization of the product from ethyl acetate–methanol gave the 7-ketone (II, 2.07 g.), plates m.p. 252–256°, $[\alpha]_D$ −6°, λ_{max}^{MeOH} 237 mμ (ε 11,000), λ_{max}^{Nujol} 2.92, 5.73, 5.88, 5.96, 6.10, 8.1, 9.08, 9.58 μ.

Anal. Calcd. for $C_{21}H_{36}O_6$: C, 64.27; H, 7.19. Found: C, 64.25; H, 7.02.

7-Methyl-4,6-pregnadiene-17α,21-diol-3,11,20-trione 21-acetate (III). A solution of 3.0 g. of II in tetrahydrofuran (150 ml.) was added dropwise to an ethereal solution of methyllithium (from 3.45 g. of lithium and 14 ml. of methyl iodide in 300 ml. of ether), with stirring under nitrogen. The addition took 45 min., and the reaction mixture was then stirred under nitrogen for 20 hr. at 25°. The mixture was then poured slowly, with stirring, into iced 6% ammonium sulphate solution (1 l.). The product, isolated by extraction with ether, then methylene chloride, was an oil [λ_{max}^{MeOH} 243; 294 mμ (ε 6000; 5000)]. This material was dissolved in 0.27 *N* methanolic perchloric acid (175 ml.)[5] and left at room temperature for 19 hr., yielding 1.83 g. of a substance showing λ_{max}^{MeOH} 293 (ε 21,000). After acetylation (pyridine and acetic anhydride overnight at room temperature) and chromatography on Florisil, there was obtained, in the benzene ether eluates, 7-methyl-4,6-pregnadiene-17α,21-diol-3,11,20-trione 21-acetate (III; 466 mg.) as needles (acetone-hexane) m.p. 199–204°, $[\alpha]_D$ +362°, λ_{max}^{MeOH} 293 (ε 25,000). λ_{max}^{Nujol} 2.95, 5.72, 5.79, 5.84, 6.05, 6.19, 6.32, 8.15 μ.

Anal. Calcd. for $C_{24}H_{30}O_6.0.5(CH_3)_2CO$: C, 69.05; H, 7.50. Found: C, 69.20; H, 7.90.

7β-Methylcortisone acetate (IV). 7-Methyl-4,6-pregnadiene-17α,21-diol-3,11,20-trione 21-acetate (III; 620 mg.) was hydrogenated in benzene (80 ml.) with palladized strontium carbonate (300 mg.) at room temperature until 1 mole of hydrogen had been absorbed. Chromatography of the product over Florisil afforded, in the benzene ether (3:2) eluates, 7β-methylcortisone acetate (IV; 173 mg.), m.p. 206–208° (from acetone-hexane), $[\alpha]_D$ +168°, λ_{max}^{MeOH} 239 mμ (ε 13,800); λ_{max}^{Nujol} 2.94, 5.78, 5.86, 6.02, 6.18, 8.12 μ.

Anal. Calcd. for $C_{24}H_{32}O_6$: C, 69.21; H, 7.74. Found: C, 69.00; H, 7.60.

7β-Methylhydrocortisone acetate (V). A solution of 7β-methylcortisone acetate (125 mg.) in methanol (5 ml.), pyridine (0.15 ml.), and water (1.25 ml.) containing semicarbazide hydrochloride (207 mg.) was refluxed for 15 hr. The solution was then concentrated *in vacuo*, diluted with water, and filtered, giving 130 mg. of 3,20-bissemicarbazone. Extraction of the filtrate with ether gave an additional 14 mg. (total yield 144 mg.). The bissemicarbazone (144 mg.) was dissolved in tetrahydrofuran (5 ml.) and water (2.5 ml.), potassium borohydride (150 mg.) was added, and the mixture was refluxed overnight. Cooling and acidification to *p*H 5.5 with acetic acid, followed by heating on the steam bath for 0.5 hr., then dilution with water, filtration, washing with water, and drying, gave 57 mg. of crude bissemicarbazone of 7β-methylhydrocortisone. Extraction of the filtrate with methylene chloride and ethyl acetate, after addition of saturated sodium chloride solution, yielded a further 22 mg. (total yield 79 mg.). The infrared spectrum of this material (Nujol) indicated substantially complete reduction of the 11-ketone group.

Cleavage of the 3,20-bissemicarbazone was now carried out by adding the steroid (79 mg.) to 14 ml. of a 3:2 chloroform-tetrahydrofuran mixture and 7.4 ml. of 1.25 *N*-hydrochloric acid. The two-phase system was stirred vigorously at room temperature for 1.5 hr. The organic phase was then separated, and the aqueous phase was extracted four times with chloroform. The chloroform extracts and the original chloroform phase were combined, washed with water, and evaporated *in vacuo* to give a solid. Acetylation overnight at room temperature with pyridine–acetic anhydride, followed by chromatography of the acetylated product furnished 7β-methylhydrocortisone acetate (V, 11 mg.), needles (from acetone-hexane) m.p. 185–190°, $[\alpha]_D$ +131°, λ_{max}^{MeOH} 243 mμ. (ε 15,000); λ_{max}^{Nujol} 3.0, 5.74, 5.82, 6.15, 8.15 μ.

Anal. Calcd. for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19. Found: C, 68.38; H, 7.94.

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Quaternary 2-Oxomorpholinium Salts[1]

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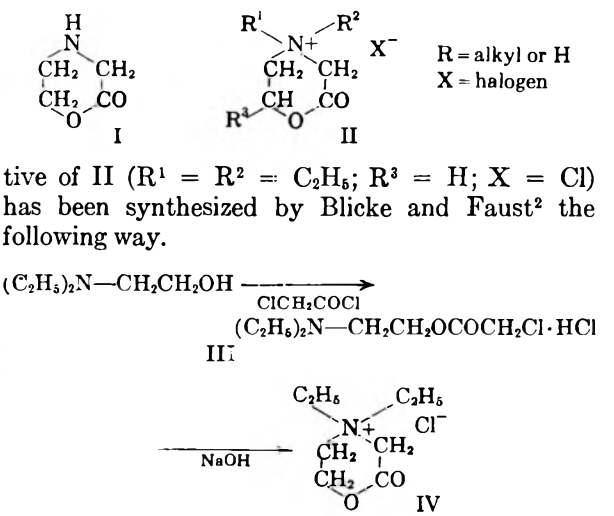
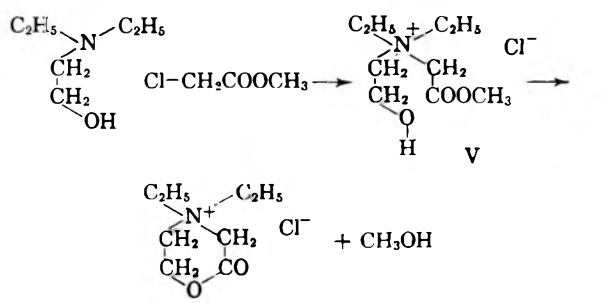
Quaternary 2-oxomorpholinium salts are based on the ring system of 2-oxomorpholine (I) which also might be called morpholactone to emphasize its lactone nature. The quaternary diethyl derivative of II ($R^1 = R^2 = C_2H_5$; $R^3 = H$; X = Cl) has been synthesized by Blicke and Faust[2] the following way.



The hydrochloride III gave 4,4-diethyl-2-oxomorpholinium chloride (IV) in a yield of 26%, m.p. 198–199.° Before the paper of Blicke and Faust appeared we had already synthesized IV and several related compounds by a condensation of β-dialkylamino alcohols and haloacetic esters. Presumably this reaction proceeds in two steps. The first step is the formation of the quaternary



(1) The larger part of these experiments has been performed at the B. F. Goodrich Research Center, Brecksville, Ohio.

(2) F. F. Blicke and J. A. Faust, *J. Am. Chem. Soc.*, **76**, 3158 (1954).

TABLE I

2-OXOMORPHOLINIUM SALTS (II)

R_1, R_2	R_3	X	Yield, %	M.P., °C.	Analysis
C_2H_5,C_2H_5	H	Cl	95	204.5–205	Calcd. for $C_8H_{16}ClNO_2$: C, 49.74; H, 8.29; N, 7.25; Cl, 18.31. Found: C, 49.53; H, 8.37; N, 7.23; Cl, 18.70
C_2H_5, C_2H_5	H	Br	94	226–227 dec.	Calcd. for $C_8H_{16}BrNO_2$: Br, 33.60. Found: Br, 33.92
CH_3, CH_3	CH_3	Cl	80	242 dec.	Calcd. for $C_7H_{14}ClNO_2$: C, 46.92; H, 7.82; N, 7.82; Cl, 19.55. Found: C, 46.99; H, 7.85; N, 7.76; Cl, 19.93
CH_3, CH_3	CH_3	Br	95	240 dec.	Calcd. for $C_7H_{14}BrNO_2$: Br, 35.71. Found: Br, 35.92
CH_3, CH_2CH_2OH	H	Cl	89	185–186	Calcd. for $C_7H_{14}ClNO_3$: C, 43.07; H, 7.17; N, 7.17; Cl, 17.94. Found: C, 42.93; H, 6.93, N, 7.20; Cl, 18.13
$CH_2CH_2OCH_2CH_2$	H	Cl	85	260–262 dec.	Calcd. for $C_8H_{14}ClNO_3$: C, 46.30; H, 6.76; N, 6.76; Cl, 16.90. Found: C, 46.12; H, 6.74; N, 6.76; Cl, 16.87
$CH_2CH_2OCH_2CH_2$	H	Br	95	247–248	Calcd. for $C_8H_{14}BrNO_3$: Br, 31.74. Found: Br, 31.60
$(CH_2)_4$	H	Br	94	227	Calcd. for $C_8H_{14}BrNO_2$: Br, 33.89. Found: Br, 33.68
$(CH_2)_5$	H	Cl	86–87	256–258	Calcd. for $C_9H_{16}ClNO_2$: N, 6.85. Found: N, 6.55

salt (V) and the second is a ring closure in which alcohol is eliminated.

Spiro-2-oxomorpholinium salts are obtained in a similar manner when cyclic aminoalcohols such as β-(*N*-pyrrolidyl)ethanol and β-(*N*-piperidyl)-ethanol are used.

The reaction is performed by heating the dialkylaminoalcohol and the haloacetic ester in a solvent such as toluene, xylene, or benzene. Only small amounts of the quaternary salts can be prepared without using a solvent because of the strongly exothermic reaction. The alcohol formed is distilled off and the precipitated quaternary salt filtered and washed with acetone. The product is then recrystallized from absolute ethanol, methanol, or isopropyl alcohol.

The alcohols (ethanol, methanol) formed during the reaction have been characterized as their 3,5-dinitrobenzoyl derivatives.

The aqueous solutions of the quaternary 2-oxomorpholinium salts have a *p*H of 3 to 4. Some of them show biologic activity and influence phagocytosis.[3]

When β-(*N*-phenyl-*N*-ethylamino)ethanol and ethyl chloroacetate were allowed to react, only quaternization was observed and no ring closure occurred. Since this behavior might be attributed to a steric hindrance of the aromatic ring we plan to extend this preliminary experiment in order to study the influence of substituents on the ring closure.

The quaternary 2-oxomorpholinium salts prepared are listed in Table I.

EXPERIMENTAL

In order to obtain good yields the starting materials, particularly the aminoalcohols, have to be freshly distilled.

4,4-Diethyl-2-oxomorpholinium chloride. Methyl chloroacetate (108 g., 1 mole), 117 g. (1 mole) of β-(*N*,*N*-diethylamino)ethanol, and 300 ml. of dry xylene were heated and stirred for 3 hr. at 120 to 130°. The methanol which formed during the reaction was continuously removed and identified as the 3,5-dinitrobenzoyl derivative (m.p. 111–112°). The precipitated quaternary salt (184 g.) was filtered, washed with acetone, and recrystallized twice from absolute ethanol.

The salt is difficultly soluble in absolute ethanol but readily soluble in 95 to 98% ethanol.

About the same yield was obtained when ethyl chloroacetate was used instead of methyl chloroacetate.

2-Oxo-3-oxa-6-azoniaspiro[4.5]decane bromide. *N*-(β-Hydroxyethyl)pyrrolidine (11.5 g., 0.1 mole) and 15.3 g. (0.1 mole) of methyl bromoacetate were heated in 40 ml. of benzene for 1 hr. at 75 to 80°. The white precipitate, 22.2 g., was recrystallized from a mixture (1:1) of absolute ethanol and methanol.

Acknowledgment. The authors wish to express their gratitude to the Analytical Department of the B. F. Goodrich Research Center for the analytical work performed.

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(3) W. J. Nungester and Ada May Ames, *J. Infectious Diseases*, **90**, 51–60 (1952).

Melibiose Monohydrate[1]

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Melibiose was originally prepared from raffinose by controlled acid hydrolysis[2] and later by the action of baker's yeast,[3,4] and was isolated, not without difficulty,[3–5] as the dihydrate, m.p. 83°; this dihydrate was the β anomer since it showed in water $[\alpha]_D^{23}$ +111.7° changing to +129.5°.[3–7]

Whereas studies reported[5,7,8] in the literature appear to have been carried out with the β form of

(1) Paper No. 3973 of the Scientific Journal Series, Minnesota Agricultural Experiment Station.

(2) C. Scheibler and H. Mittelmeier, *Ber.*, **22**, 1678 (1889); **23**, 1438 (1890).

(3) M. Berthelot, *Z. Ver. Zuckerind.*, **39**, 1078 (1902).

(4) D. Loiseau, *Z. Ver. Zuckerind.*, **40**, 1050 (1903).

(5) C. S. Hudson and T. S. Harding, *J. Am. Chem. Soc.*, **37**, 2734 (1915).

(6) A. Bau, *Z. Ver. Zuckerind.*, **41**, 481 (1904).

(7) C. S. Hudson and E. Yanowsky, *J. Am. Chem. Soc.*, **39**, 1013 (1917).

(8) W. N. Haworth, J. V. Loach, and C. W. Long, *J. Chem. Soc.*, 3146 (1927).

melibiose dihydrate, chemical storehouses at the present time evidently supply what is sometimes referred to as a "monohydrate" or a "hydrate," but there is no evidence as to its anomeric form.

We have recently repeated the preparation of melibiose by the above method[9] using yeast, expecting to obtain the dihydrate, but instead we have obtained a monohydrate, m.p. 179–181°. This monohydrate of melibiose is evidently the α anomer since it shows $[\alpha]_D^{23}$ +157° changing to +137° in water (C, 1.0).

Anal. Calcd. for $C_{12}H_{22}O_{11} \cdot H_2O$: C, 40.00; H, 6.71. Found: C, 39.95; H, 6.60.

When allowance was made for the change in molecular weight, the equilibrium rotation of +137° found for the new monohydrate agreed well with the value of +129.5° reported for the dihydrate.

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(9) "Polarimetry Saccharimetry and the Sugars," Circular C440 of the Natl. Bur. Standards, by Frederick J. Bates and Associates, 1942, p. 473.

Some Derivatives of *p*-Bis(β-hydroxyethyl)-aminobenzaldehyde

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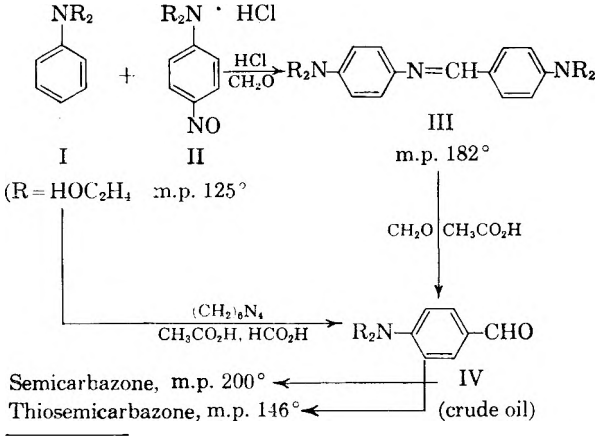
Although several *p*-dialkylaminobenzaldehyde derivatives are reported in the literature, including the butyl- and ethyl-β-hydroxyethyl- compounds,[2] the bis(β-hydroxyethyl) analog apparently has not been reported. Using a procedure similar to that for the preparation of *p*-dimethylaminobenzaldehyde,[3] it has not been possible to obtain a purified sample of the bis(β-hydroxyethyl) compound, although several derivatives of it have been isolated and identified.



EXPERIMENTAL[4]

p-Nitroso-bis(β-hydroxyethyl)aminobenzene hydrochloride (II). A stirred solution of 36.2 g. of bis(β-hydroxyethyl)-aniline in a mixture of 20 ml. of water and 40 ml. of concentrated hydrochloric acid was cooled in an ice-salt bath and a solution of 14.6 g. of sodium nitrite in 25 ml. of water was added, care being taken that the temperature did not rise above 5°. After stirring for a further period of 30 min., the orange crystalline nitroso compound was collected, washed with 40 ml. of cold 1:1 hydrochloric acid and dried first in air and then in a desiccator. On recrystallization from ethanol the compound melted with decomposition at 123–125°.

Anal. Calcd. for $C_{10}H_{15}N_2O_3Cl$: C, 48.68; H, 6.13; N, 11.36. Found: C, 48.33; H, 6.30; N, 11.16.

The nitroso compound seemed to be sensitive to light. The original color soon changed to greenish yellow and finally to black within a few days.

N-[p'-Bis(hydroxyethyl)aminobenzylidene]-p-[bis(hydroxyethyl)amino]-aniline (III). Wet nitroso hydrochloride, from a preparation using four times the quantities described above, was added all at once to a 5-liter beaker containing a solution made by warming for 10 min. on a steam bath a mixture of 173.6 g. of bis(β-hydroxyethyl)aniline, 192 ml. of concentrated hydrochloric acid and 100 ml. of 40% formaldehyde solution. The initial vigorous reaction soon subsided. After allowing the mixture to stand for an hour, about 1600 g. of crushed ice was added to the mixture and it was cautiously neutralized with a very slight excess of 40% sodium hydroxide solution. The aqueous portion was poured off from the plastic mass, which was washed by trituration and decantation with four 3.5-l. portions of cold water, care being taken to see that the wash liquor before decantation was neutral. The temperature throughout the latter operation was maintained below 15°. The plastic mass was warmed with 400 ml. of hot ethanol, seeded (a portion of the solution, diluted with 2–3 times its volume of ether, on cooling, scratching, and washing with cold ethanol gave the desired material for seeding) and cooled thoroughly, when yellow crystalline material separated. This was collected and washed with cold ethanol to yield 105 g., m.p. 176–178°. One recrystallization from ethanol raised the melting point to 181–182°.

Anal. Calcd. for $C_{21}H_{29}N_3O_4$: C, 65.09; H, 7.54; N, 10.86. Found: C, 64.77; H, 7.67; N, 10.83.

p-Bis(β-hydroxyethyl)aminobenzaldehyde semicarbazone. Compound III (27 g., 0.7 mole) was stirred at room temperature with a mixture of 42 ml. of glacial acetic acid and 40% formaldehyde for 4 hr. This mixture was then diluted with 70 ml. of water, cooled thoroughly, cautiously basified with a slight excess of ammonia, and extracted with chloroform in a liquid-liquid extractor for 16 hr. After drying and evaporation of solvent, the residual oil, containing some high-melting by-product, weighed 15.6 g. This oil, presumably the crude aldehyde (IV), could not be crystallized and did not distill at 285° (0.05 mm.). The *semicarbazone*, prepared in the usual way using sodium acetate, readily recrystallized from ethanol, m.p. 199–200°, dec.

Anal. Calcd. for $C_{12}H_{18}N_4O_3$: C, 54.12; H, 6.81; N, 21.04. Found: C, 54.08; H, 7.16; N, 21.32.

p-Bis(β-hydroxyethyl)aminobenzaldehyde thiosemicarbazone. (a) To a solution of 11 g. of the crude oil containing the aldehyde (IV) in 20 ml. of 95% ethanol and 60 ml. of water, 4.8 g. of thiosemicarbazide was added. After heating under reflux for 4 hr., the mixture was cooled and the supernatant liquor was decanted from the oily precipitate. After addition of 200 ml. of hot water, the mixture was heated to boil-

(1) Supported by U. S. Public Health Service Grant No. CY-2189.

(2) J. F. J. Dippy, L. T. Hogarth, H. B. Watson, and F. R. Williams, *J. Soc. Chem. Ind.*, 56, 3467 (1937).

(3) R. Adams and G. H. Coleman, *Org. Syntheses*, Coll. Vol. I, 214 (1941).

(4) Analyses by Midwest Microanalytical Lab., Indianapolis.

ing. On slow cooling to room temperature, the thiosemicarbazone crystallized; yield, 4.5 g., m.p. 144–146°. After recrystallization from ethanol, the compound melted at 146–147°.

Anal. Calcd. for $C_{12}H_{18}N_4O_2S$: C, 51.05; H, 6.42; N, 19.85; S, 11.33. Found: C, 51.12; H, 6.65; N, 19.72; S, 10.65, 10.57.

(b) A mixture of 18.1 g. of bis(β-hydroxyethyl)aniline, 20 g. of hexamethylenetetramine and 10 ml. of ethanol was heated under reflux. After 15 min., 15 ml. of a mixture of 22.5 ml. of acetic acid and 22.5 ml. of formic acid was added. The remainder was added at 30-min. intervals in 5-ml. portions. After heating for another 3 hr., the reaction mixture was poured into a solution of 12.5 ml. of concentrated hydrochloric acid and 300 ml. of water. After standing overnight, the green solution was cooled, basified with a slight excess of concentrated sodium hydroxide solution and extracted with one 100-ml. and one 50-ml. portion of chloroform. The aqueous portion was saturated with sodium chloride and again extracted with three 50-ml. portions of chloroform. The combined extract was dried with magnesium sulfate and the chloroform was removed. The residual viscous material weighed 17.5 g. This was converted to the thiosemicarbazone essentially as described above; yield, 5.2 g. The two products were identical.

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Synthesis of 2,3-Cyclopenteno-7*H*-benzo[*c*]-fluorene

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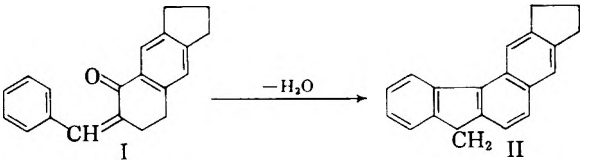
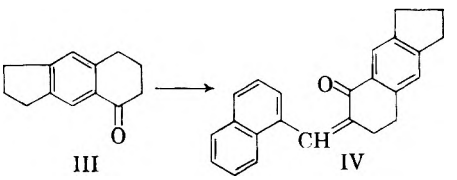
It is well known that whereas benz[*a*]anthracene is at the most only weakly carcinogenic,[1] 9,10-cyclopentenobenz[*a*]anthracene shows pronounced carcinogenic activity.[2] Hence it was of interest to synthesize 2,3-cyclopenteno-7*H*-benzo[c]fluorene (II) for biological testing, although the parent compound, 7*H*-benzo[*c*]fluorene had already proved inactive.[3] A further point of interest is the possibility for polycyclic fluorenes of this type to act as antagonists of carcinogens as is the case with 13*H*-dibenzo[*ag*]fluorene.[4]

Hydrocarbon II was now readily prepared by cyclodehydration by means of phosphorus pentoxide,[5] of 2-benzylidene-6,7-cyclopenteno-1-tetralone (I).

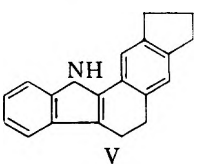
This last compound was readily prepared by alkali-catalyzed condensation of benzaldehyde with



6,7-cyclopenteno-1-tetralone (III), which was obtained from hydrindene by means of the succinic anhydride method.[6] Similar condensation of ketone III with 1-naphthaldehyde furnished 2-(1-naphthylmethylene)-6,7-cyclopenteno-1-tetralone (IV), which, on treatment with phosphorus pentoxide, gave a compound m.p. 249°, in insufficient quantity for analytical determination.



Fischer indolization of the phenylhydrazone of ketone III afforded 5,6-dihydro-2,3-cyclopenteno-11*H*-benzo[*a*]carbazole (V).



Compounds II and V are undergoing biological tests in this Institute, and results will be reported later.

EXPERIMENTAL

Preparation of ketone III. The succinoylation of hydrindene[6] was performed with 50 g. of the hydrocarbon, 42.3 g. of succinic anhydride, and 85 g. of aluminum chloride in 250 ml. of nitrobenzene, and the mixture left for 18 hr. at room temperature prior to the usual treatment. The yield of the γ-keto acid, m.p. 128°, was 60 g. Reduction to the corresponding γ-(5-hydrindyl)butyric acid, b.p. 210–215°/15 mm., m.p. 51°, was effected with hydrazine hydrate and potassium hydroxide in diethylene glycol, and cyclization of the acid chloride (prepared from thionyl chloride) was performed with aluminum chloride in carbon disulfide in the cold (48 hr. standing), giving an 80% yield of ketone III, b.p. 182–183°/12 mm.

2-Benzylidene-6,7-cyclopenteno-1-tetralone (I). A solution of 3.5 g. of the above ketone and 2 g. of freshly redistilled benzaldehyde in 20 ml. of warm ethanol was shaken with a few drops of 20% aqueous potassium hydroxide. The crystalline mass which rapidly formed was filtered off after cooling, washed with water, and recrystallized from ethanol. Yield: 2.8 g. of shiny yellowish prisms, m.p. 128°, giving an orange halochromism with sulfuric acid.

Anal. Calcd. for $C_{20}H_{18}O$: C, 87.6; H, 6.6. Found: C, 87.4; H, 6.6.

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2,3-Cyclopenteno-7H-benzo[c] fluorene (II). To a solution of 2.5 g. of the foregoing ketone in 30 ml. of anhydrous xylene, 2.6 g. of finely powdered phosphorus pentoxide was added in small portions, and the mixture was refluxed for 30 hr. After cooling, water was added, and the dark fluorescent xylene solution was washed with aqueous sodium hydroxide, then with water, and dried over sodium sulfate; the solvent was then distilled off and the residue vacuum-fractionated. The thick yellow oil, b.p. 220–225°/0.4 mm. was taken up in ethanol containing some drops of benzene, and the solid precipitate obtained was recrystallized from ethanol, giving shiny colorless needles, m.p. 140° (no coloration with cold sulfuric acid). Yield: 30%.

Anal. Calcd. for $C_{20}H_{16}$: C, 93.7; H, 6.3. Found: C, 93.4; H, 6.3.

The corresponding picrate crystallized from ethanol in orange-red prisms, m.p. 184°.

Anal. Calcd. for $C_{26}H_{19}N_3O_7$: N, 8.7. Found: N, 8.4.

2-(1-Naphthylmethylene)-6,7-cyclopenteno-1-tetralone (IV). A solution of 0.35 g. of ketone III and 0.3 g. of 1-naphthaldehyde in 3 ml. of warm ethanol was treated with one drop of 20% aqueous potassium hydroxide; the solid precipitate formed on cooling crystallized from ethanol in shiny yellowish prisms (0.35 g.), m.p. 115°, giving a deep red halochromism with sulfuric acid.

Anal. Calcd. for $C_{24}H_{20}O$: C, 88.9; H, 6.2. Found: C, 88.6; H, 6.3.

Treatment of this ketone with phosphorus pentoxide in xylene as for the above hydrocarbon, afforded a compound which crystallized from a mixture of ethanol and benzene in shiny colorless leaflets, m.p. 249°, which gave no picrate.

5,6-Dihydro-2,3-cyclopenteno-11H-benzo[a]carbazole (V). A mixture of 3.5 g. of ketone III and 3 g. of phenylhydrazine was heated at 120° until steam had ceased to be evolved; on cooling, 30 ml. of acetic acid saturated with hydrogen chloride was added. The mixture was brought to the boil, poured into water, and the indolization product taken up in benzene; the benzene solution was washed with dilute aqueous sodium hydroxide, then with water, dried over sodium sulfate, the solvent removed, and the residue vacuum-distilled. The portion boiling above 250°/12 mm. crystallized from ethanol in colorless prisms (2.5 g.), m.p. 204°.

Anal. Calcd. for $C_{19}H_{17}N$: N, 5.4. Found: N, 5.2.

The corresponding picrate crystallized from ethanol in shiny, deep violet prisms, m.p. 194°.

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Selective Reduction of a Benzyloxyamino Group in the Presence of a Nitro Group[1]

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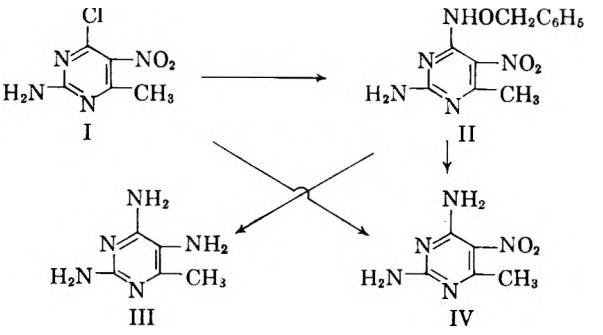
In the course of experiments directed towards the synthesis of purine-9-oxides, selective reduction of the nitro group in 2-amino-4-benzyloxyamino-5-nitro-6-methylpyrimidine (II) was attempted. This could not be achieved, but conditions have been found for the selective reduction of the benzyloxyamino group.



Reaction of II with hydrazine in the presence of Raney nickel, with ferrous hydroxide or with hydrogen in the presence of palladium catalyst resulted in complete reduction to 2,4,5-triamino-6-methylpyrimidine (III). Unexpectedly, however, reduction with aqueous ethanolic ammonium sulfide gave 2,4-diamino-5-nitro-6-methylpyrimidine (IV), identical with the reaction product of 2-amino-4-chloro-5-nitro-6-methylpyrimidine (I) with ethanolic ammonia.

The steric environment of the nitro group in II probably contributes to the selectivity of the latter reduction. These experiments emphasize the ease of reduction of the benzyloxy grouping under neutral or alkaline conditions where hydrolysis of the group does not occur.

EXPERIMENTAL[2]

2-Amino-4-benzyloxyamino-5-nitro-6-methylpyrimidine (II). To a solution of 9.5 g. of 2-amino-4-chloro-5-nitro-6-methylpyrimidine[3] in 200 ml. of ethanol was added 8.0 g. of benzyloxyamine[4] and 8.5 g. of powdered anhydrous sodium acetate. The mixture was heated under reflux for 1 hr., the solvent removed under reduced pressure and the residue triturated with water. The yellow solid which separated was collected by filtration and recrystallized from ethanol to give 12.0 g. (78%) of fine yellow needles, m.p. 191–192°.

Anal. Calcd. for $C_{12}H_{13}N_5O_3$: C, 52.4; H, 4.7; N, 25.45. Found: C, 52.6; H, 4.9; N, 25.3.

2,4,5-Triamino-6-methylpyrimidine (III). Method *a*. A suspension of 2 g. of powdered 2-amino-4-benzyloxyamino-5-nitro-6-methylpyrimidine in 200 ml. of ethanol was treated with 2 ml. of 96% hydrazine followed by a small amount of Raney nickel catalyst. The resulting mixture was heated under reflux for 20 min., filtered, and the filtrate evaporated to dryness. Recrystallization of the residue from ethanol yielded 0.65 g. (64%) of small tan prisms, m.p. 242–244°. This material is reported to melt at 243°[5] and 241–243°.[6]

(1) This investigation was supported by a grant from the American Cancer Society.

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Method *b*. To a stirred solution of 18.5 g. of hydrated ferrous sulfate in 300 ml. of water at 75° was added 27 g. of hydrated barium hydroxide. After 15 min., 2 g. of powdered 2-amino-4-benzyloxyamino-5-nitro-6-methylpyrimidine was added, the mixture stirred, and the temperature raised to 100° for 20 min. The hot solution was filtered and the filter cake was extracted with boiling water. The combined filtrates were evaporated to dryness under reduced pressure and the residue recrystallized from ethanol to give 0.81 g. (79.5%) of pale brown prisms, m.p. 241–243°, identical with the product obtained by method (*a*) above.

2,4-Diamino-5-nitro-6-methylpyrimidine (IV). Method *a*. A suspension of 2 g. of 2-amino-4-benzyloxyamino-5-nitro-6-methylpyrimidine in 20 ml. of ethanol and 20 ml. of concentrated ammonium hydroxide was saturated with hydrogen sulfide and then heated under reflux for 30 min. Addition of 60 ml. of water followed by cooling caused the separation of a yellow solid which was collected by filtration and dissolved in dilute hydrochloric acid. Extraction of this acidic solution with methylene chloride removed a small amount of oily material. Neutralization of the aqueous layer with dilute ammonium hydroxide precipitated a yellow solid which was recrystallized from ethanol to give 0.9 g. (73%) of yellow needles, m.p. 235–236°. A mixture melting point determination with a sample of authentic 2,4-diamino-5-nitro-6-methylpyrimidine prepared as described below showed no depression. The reported melting point for a crude sample of this material is 235° dec.[7]

Method *b*. A solution of 2 g. of 2-amino-4-chloro-5-nitro-6-methylpyrimidine in 125 ml. of ethanol was saturated with dry ammonia and then heated under reflux for 2 hr. while ammonia was passed continually through the refluxing solution. The reaction mixture was cooled overnight and filtered to give 1.4 g. of crude product, m.p. 237–240°. A further quantity (0.2 g.) was obtained by concentration of the filtrate. Recrystallization of the combined crude products from ethanol yielded 1.45 g. (80.5%) of yellow needles, m.p. 235–236°.

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Effect of Molecular Size and Structure on the Pyrolysis of Esters. II[1]

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It has been demonstrated that a change in the size of the acyl portion of esters causes a change in the ease of their pyrolysis.[1] For example, esters of stearic acid pyrolyze at a lower temperature than esters of acetic or formic acid. The decrease, however, in the temperature of pyrolysis as the acyl portion increases in size by one methylene group is not a regular decrease; rather it decreases in a zigzag fashion with esters from acids of an even number of carbon atoms being slightly more stable than their neighboring homologues.

The question as to whether this effect is due to a change in the size of the acyl portion or a change in the molecular weight of the ester was not answered.

Nine isomeric normal aliphatic primary esters of molecular weight 200 and formula $C_nH_{2n+1}CO_2C_mH_{2m+1}$ (n + m = 12) have been pyrolyzed under conditions identical to those reported in the earlier study. The results from this study clearly demonstrate that the ease of pyrolysis of esters is a function of molecular weight (or size) of the ester and not of the acyl portion alone.

In comparing the ease of pyrolysis of the nine esters their "characteristic temperatures"[2] were determined by passing a constant amount at a definite rate through a flow system and measuring the extent of pyrolysis at seven different temperatures over a range of 81°. The extent of pyrolysis in this temperature range was from 6.9 to 96.3 per cent. All esters studied showed a characteristic

TABLE I

PYROLYSIS OF ALKANOATES OF THE FORMULA $C_nH_{2n+1}CO_2C_mH_{2m+1}$

Name	Yield, %	B.p. °C.	B.p. Mm.	n_D	d_{20}^{20}	Analysis: Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Characteristic Temp., °C.	Yield, % at C.T.
Ethyl decanoate	83	114–116[a]	20	1.4257[b,c]	0.8708[b,d]					561	
Propyl nonoate	82	127–129[e]	21	1.4236[f,g]	0.8637[h]					562	94.7
Butyl octanoate	93	122–125[i]	20	1.4229[f,j]	0.8646					558	95.5
Pentyl heptanoate	87	120–126[k]	20	1.4233[f,l]	0.8632					562	92.0
Hexyl hexanoate	93	125–126	20	1.4249[b]	0.8630[m]	71.95	71.79	12.08	11.79	561	93.0
Heptyl pentanoate	91	124–126	20	1.4248[b]	0.8610[n]	71.95	72.08	12.08	11.87	560	92.4
Octyl butanoate	75	120–123	19	1.4250[b]	0.8621[o]	71.95	72.00	12.08	11.96	560	91.3
Nonyl propanoate	85	126–128	20	1.4259[b]	0.8637	71.95	72.02	12.08	11.91	559	94.8
Decyl acetate	88	126–127[p]	20	1.4272[b,q]	0.8654[r]					561	96.3

[a] Reported[3] b.p. 122–124°/13 mm. [b] 20°. [c] Reported[4] n_D^{45} 1.4154. [d] Reported[5] d_4^{20} 0.862. The low yield (14.4%) in the pyrolysis of this ester was demonstrated to be caused by contamination of the ethyl decanoate with methyl decanoate by conversion to the 3,5-dinitrobenzoate, m.p. 107–108°. The methyl ester is stable to pyrolysis at this temperature. [e] Reported[6] b.p. 120–122°/20 mm. [f] 25°. [g] Reported[6] n_D^{25} 1.4236. [h] Reported[6] d_4^{25} 0.8540. [i] Reported[6] b.p. 121–122°/20 mm. [j] Reported[6] n_D^{25} 1.4232. [k] Reported[6] b.p. 118–119°/20 mm. [l] Reported[6] n_D^{25} 1.4231. [m] Reported[7] d^{30} 0.85414. [n] Reported[7] d_4^{15} 0.86625. [o] Reported[7] d_4^{15} 0.86686. [p] Reported[8] b.p. 125–126°/15 mm. [q] Reported[9] n_D^{20} 1.4272. [r] Reported[10] d_4^{20} 0.8671.

(1) Previous paper in this series, *J. Am. Chem. Soc.*, 79, 875 (1957).

(2) The "characteristic temperature" has been defined[1] as the temperature at which a maximum is obtained from a plot of percentage yield divided by pyrolysis temperature *vs.* the pyrolysis temperature. In effect the characteristic temperature is that temperature at which the most efficient pyrolysis takes place when the rate of flow is constant.

temperature between 558–562 ± 1°. A titration of the acid and a measure of the carbon dioxide formed (which at no time was greater than 2.8%) served to determine the extent of pyrolysis. The esters were prepared according to the method of Brändström,[3] and the data on their preparation, identification, and pyrolysis are given in Table I.

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Methadon Analogs[1]

SEYMOUR L. SHAPIRO, HAROLD SOLOWAY, AND LOUIS FREEDMAN

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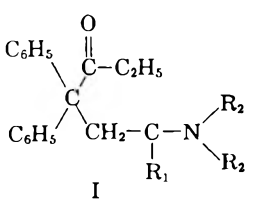
Variations in the structure of methadon [I, R_1 = CH_3, NR_2 = $N(CH_3)_2$] have been made[2,3] without



I

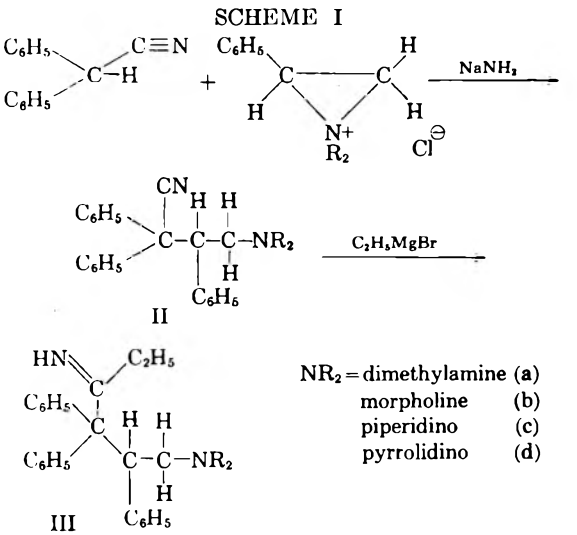
substantial increase in activity, and often with loss of activity. Thus substitution in I (R_1 = C_2H_5) resulted in disappearance of activity,[4] while substitution of $-NR_2$ as morpholine or piperidine afforded retention of analgesic acitvity.[3] Recent studies have critically examined the structural features of methadon analogs which influence activity.[5]

This paper reports the isolation of 1-substituted amino-2,3,3-triphenylhexanimines in the attempted synthesis of I (R_1 = C_6H_5) from the previously described 2-dialkylamino-1-phenethyl chlorides.[6]

The sequence of reactions used is reported as shown in Scheme I.

In earlier work with methadon analogs, the condensation of dialkylaminoisoalkyl chlorides with diphenylacetonitrile has been shown to proceed *via* an ethyleneimonium ion[7] with subsequent reaction at the imonium ion being governed[8] by steric factors, as well as polar factors, both

SCHEME I



within the cyclic ion and in the diphenylacetonitrile anion with which it reacts.

The imonium ion obtained from the 2-dialkylamino-1-phenethyl chlorides would in all probability be more vulnerable to nucleophilic attack[6] by the diphenylacetonitrile anion at the phenyl-bearing carbon to yield the 2,2,3-triphenyl-4-substituted aminobutyronitrile (II). Only one compound was isolable in these condensations. The likelihood of reaction being effected at this more hindered carbon of the imonium ion, is also consistent[9] with the isolation of the ketimines (III).

Considerable difficulty was initially experienced in the isolation of the butyronitriles (II) in view of their unanticipated failure to be extracted into aqueous solvents as their hydrochlorides. The steric influence of the 3-phenyl group in such nitriles is apparent when one considers the ease of hydrochloride formation in analogous compounds wherein

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TABLE I

2,2,3-TRIPHENYL-4-DIALKYLAMINOBUTYRONITRILES (II)
$(C_6H_5)_2C(CN)CH(C_6H_5)CH_2NR_2$

Compounds	NR_2	M.P., °C.[a,b]	Yield, %	Formula[d]	Analyses[c] Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
IIa	Dimethylamino	193–195	33	$C_{24}H_{24}N_2$	84.7	84.7	7.1	6.9	8.2	8.0
IIb	Morpholino	178–180	37	$C_{26}H_{26}N_2O$	81.6	81.8	6.9	6.7	7.3	7.1
IIc	Piperidino	180–184[b1]	47	$C_{27}H_{28}N_2$	85.2	85.3	7.4	7.4	7.4	7.1
IId	Pyrrolidino	187–189[b2]	47	$C_{26}H_{26}N_2$	85.2	84.9	7.2	7.1	7.7	7.9
	ETHYL 1,1,2-TRIPHENYL-3-DIALKYLAMINOPROPYL KETAMINES (III) AND RELATED COMPOUNDS									
IIIb	Morpholino	178–181	46	$C_{28}H_{32}N_2O$					6.8	6.7
IIIb[e]	Morpholino	222–226[b3]	52	$C_{29}H_{35}ClN_2O_2$[d1]					5.6	5.8
IIIb[f]	Morpholino	242–245[b4]	25	$C_{28}H_{32}ClNO_2$[d2]	74.7	75.2	7.2	7.3	3.1	3.0
IIIb[g]	Morpholino	64–66[b5]	47	$C_{28}H_{34}N_2O$	81.2	81.2	8.3	8.1	6.8	6.7
IIIb[h]	Morpholino	188–194[b5]		$C_{23}H_{38}Cl_2N_2O_3$[d3]	66.6	66.9	7.6	7.6	5.6	5.4
IIIb[i]	Morpholino	195–197[b1]		$C_{30}H_{34}N_2O_2$	78.9	78.4	8.0	7.7	6.1	6.0
IIIc	Piperidino	181–183	53	$C_{29}H_{34}N_2$					6.7	6.8
IIId[j]	Pyrrolidino	225–227	65	$C_{28}H_{34}Cl_2N_2$[d4]	71.8	71.3	7.1	6.9	6.0	6.2

[a] Melting points are not corrected. [b] Recrystallizing solvent is ethanol unless otherwise shown; [b1] ethyl acetate–hexane; [b2] ethyl acetate; [b3] *n*-propanol; [b4] washed with isopropyl alcohol; [b5] not recrystallized. [c] Analyses by Weiler and Strauss, Oxford, England. [d] Chlorine. Calcd.-Found;[d1] 7.4–7.4; [d2] 7.9–7.7; [d3] 14.0–14.0; [d4] 15.1–14.9. [e] Hydrochloride monohydrate. [f] Hydrochloride of ethyl 1,1,3-triphenyl-3-morpholinopropyl ketone. This compound was isolated in one run following procedures shown in the experimental for preparation of the ketimines. Repetition of the Grignard synthesis yielding a ketone with the morpholino nitrile IIb or with the other nitriles was not successful. [g] 4-Amino-1-morpholino-1,3,3-triphenylheptane. [h] Dihydrochloride-monohydrate of compound of footnote *g*. [i] *N*-Acetyl derivatives of compound of footnote *g*. [j] Dihydrochloride.

this phenyl group is replaced by methyl.[10] Steric hindrance wherein the basic constituent is modified so that it cannot accept a proton has been reported in other systems.[11,12]

The Grignard reaction using ethylmagnesium bromide[13] with II, resulted only in recovery of the reactant nitrile (IIa), and in formation of the ketimines (IIIb, IIIc, and IIId). In one experiment, a compound giving the analysis of the desired ketone corresponding to IIIb was obtained but this could not be repeated. In contrast to the nitriles (II), the ketimines (III) readily formed hydrochlorides. The failure of the *N*-4-dimethylamino-2,2,3-triphenylbutyronitrile (IIa) to condense is consistent with a conformation of the *N*-methyl groups blocking attack by the Grignard reagent at the nitrile group. In contrast, the more sterically restrained *N*-methylene carbons in IIb, IIc, and IId permit the reaction of conversion to the ketimine to occur.

The isolation of ketimines has been previously noted, particularly in the more hindered isomethadon structure[7,9,14–16] and these could be converted to the desired ketones by acid hydrolysis. The ketimines (III) of this work did not respond to hydrolysis using hydrochloric acid reflux, or under sealed tube hydrolysis using concentrated hydrochloric acid, or mixture of hydrochloric acid and acetic acid. The role of steric factors in resistance to ketimine hydrolysis has been previously explored[17,18] with the compounds of type III being substantially invulnerable to hydrolysis. Construction of molecular models indicates complete shielding of the ketimine carbon. It is also relevant that the presence of substituents on the carbon beta to the ketimine group would markedly repress hydrolysis.[19,20]

The morpholino ketimine (IIIb) was reduced to the corresponding amine with lithium aluminum hydride, which in turn was converted to the acetate.

The compounds prepared have been described in Table I.

Pharmacologic evaluation of the ketimines (III) indicated analgesic activity of the order of 1/5 that of methadon for the morpholino derivatives (IIIb), the other compounds being inactive.

EXPERIMENTAL[21,22]

N-4-Morpholino-2,2,3-triphenylbutyronitrile (IIb). A stirred suspension of 7.8 g. (0.2 mole) of sodamide in 30 ml. of tolu-

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ene was maintained at 35° in a nitrogen atmosphere during the 1-hr. addition of a solution of 39 g. (0.2 mole) of diphenylacetonitrile in 100 ml. of toluene. After the addition was complete the reaction mixture was heated under reflux for 3.5 hr., cooled, and 0.7 g. of sodium iodide added. A solution of 2-(4-morpholino)-1-phenethyl chloride [prepared from an aqueous solution of 53 g. (0.2 mole) of the hydrochloride,[6] rendered alkaline with 40% sodium hydroxide, followed by extraction of the liberated base with three 75-ml. portions of toluene which were combined and dried with magnesium sulfate] in toluene was added over 2 hr., maintaining the temperature below 35°. The reaction mixture was heated under reflux for 1.5 hr., cooled to 20°, and treated with 200 ml. of water. At this point some product precipitated and was separated. The toluene layer was separated and the aqueous phase re-extracted with 100 ml. of toluene. The initial precipitate and all toluene fractions were combined and the toluene evaporated. The residue of IIb, triturated with 100 ml. of ethanol, yielded 39 g. (51%).

1-Piperidino-2,3,3-triphenylhexanimine-4 (IIIc). A solution of ethyl magnesium bromide was prepared from 1.2 g. (0.05 mole) of magnesium and 6.5 g. (0.06 mole) of ethyl bromide in 50 ml. of anhydrous ether and treated while refluxing with a solution of 15.2 g. (0.04 mole) of IIc in 90 ml. of hot tetrahydrofuran (dried over calcium hydride) over 1 hr., followed by 60 ml. of hot xylene. During the addition, the internal temperature was raised to 80–85° by partial distillation and so maintained with stirring for 5 hr. Then 40 ml. of 1:1 hydrochloric acid was added with continued heating over 0.5 hr. Dilution with water and standing afforded the crude, sparingly soluble hydrochloride, 17 g., which was converted to the free base with aqueous sodium hydroxide.

4-Amino-1-morpholino-2,3,3-triphenylhexane (IIIb[9], Table I). A refluxing solution of 0.42 g. of lithium aluminum hydride in 50 ml. of ether under nitrogen atmosphere continuously extracted a charge of 4.2 g. (0.01 mole) of IIIb over a period of 20 hr.[23] The cooled, stirred mixture was treated slowly with 35 ml. of 10% aqueous sodium hydroxide, the ether phase decanted, and the aqueous alkaline phase continuously extracted with 100 ml. of ether. The ether extracts were combined, dried over anhydrous magnesium sulfate, filtered, and treated with dry hydrogen chloride, yielding the hydrochloride 2.3 g. (47%), m.p. 188–194°. The hydrochloride was converted to the free base which melted at 64–66°.

The *acetate*[24] was prepared, m.p. 195–197° (hexane–ethyl acetate).

Attempted hydrolysis of ketimines (III). Three g. of IIIb hydrochloride was refluxed for 36 hr. with 30 ml. of hydrochloric acid. Solution was never effected and the IIIb hydrochloride was recovered unchanged.

One g. of IIId hydrochloride and 10 ml. of hydrochloric acid in a sealed tube was maintained at 100° for 2 hr. Solution was never complete, and 0.7 g. of IIId hydrochloride was recovered.

One g. of IIId hydrochloride in 2 ml. of acetic acid and 10 ml. of hydrochloric acid in a sealed tube was maintained at 100° for 6 hr. Solution of IIId in the acid mixture was readily obtained, but only the reactant IIId hydrochloride (0.7 g.) could be recovered.

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(21) Data shown in Table I are not reproduced in the Experimental section.

(22) Representative examples are shown for the general procedures used.

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5-Phthalimido-2-tetralone[1]

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Reported here is the preparation of 5-phthalimido-2-tetralone. Some synthetic paths leading to tricyclic diterpenes and related compounds using this tetralone were initiated. Unfortunately, that work was interrputed and no further efforts in that area are now contemplated by us. However, there is continued interest and activity in such synthetic problems by other workers. We believe this tetralone and its method of preparation may be of use to others; apparently it is the only 2-tetralone carrying an amino (or potential amino) group so far prepared.

2-Methoxy-5-naphthylamine[2] (I) was reduced with sodium and alcohol in liquid ammonia. The resulting dihydro compound (enol ether) could be isolated and purified, but for convenience and obtaining maximum yield of the desired ketone, the amine was not isolated, but converted to a phthalimide derivative and subsequently to the 2-tetralone. The resulting 5-phthalimido-2-tetralone was thus obtained in 63% yield from I. The free amino group apparently is not compatible with the keto group; cleavage of the enol ether without blocking the amino group or reduction of the corresponding amino phenol with sodium and alcohol in liquid ammonia gave what appeared to be a polymeric material. The amino group could be converted to an acetamide, but the yield was not as satisfactory as with the phthalimide protecting group.

EXPERIMENTAL[3]

5-Phthalimido-2-tetralone. Sodium (35 g.) was added slowly over a period of 1.5 hr. to a solution of 6-methoxy-1-naphthylamine[2] (100 g.) in liquid ammonia (900 ml.) and 95% ethanol (130 ml.). Water (1 l.) was then added and the mixture extracted with four portions of benzene (total vol., 1 l.). The benzene extract was washed with water and then added to a solution of phthalic anhydride (100 g.) in hot benzene (1.5 l.) which resulted in an immediate precipitate of the phthalamic acid. This crude acid (164 g., m.p. 147–150° dec.) was not purified, but was converted directly to the phthalimide by refluxing a solution of it in glacial acetic acid (500 ml.) for 2 hr. To the hot acetic acid solution was added 5% hydrochloric acid (100 ml.) and after 2 min. the mixture was poured onto ice (2.5 kg.).[4] The precipitated tetralone was separated by filtration, dried (wt., 137 g.), ground to a fine powder, and stirred for 24 hr. with a solution of sodium bisulfite (665 g.) in water (1.2 l.) and 95% ethanol (300 ml.). The addition product was separated by filtration, dried, washed with chloroform, suspended in

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(3) Melting points for analytical samples are corrected; other melting points are uncorrected.

water (3 l.), and finally decomposed with solid sodium carbonate to regenerate the ketone. This was isolated by filtration, washed with water and very dilute acid, dried, and recrystallized from benzene. 5-Phthalimido-2-tetralone, 105 g., 63% yield, was obtained as colorless prisms, m.p. 200–202°. These crystals tenaciously retained traces of the benzene solvent. The analytical sample was recrystallized from a mixture of chloroform and methanol as colorless needles, m.p. 202–204°.

Anal. Calcd. for $C_{18}H_{13}O_3N$: C, 74.21; H, 4.50; N, 4.81. Found: C, 74.48; H, 4.35; N, 4.64.

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(4) In this sequence, the period of refluxing for conversion of the phthalamic acid to the phthalimide is not critical, but the time required for cleavage of the enol ether is. The acetic acid solution may be refluxed indefinitely beyond the 2 hour period suggested without impairment of yield. For the aqueous hydrochloric acid treatment, however, the yield of 5-phthalimido-2-tetralone falls off fairly rapidly with periods appreciably more than 2 minutes, and with shorter periods cleavage of the enol ether is not complete.

The Mesomorphic State. Phototropy of *p-n*-Nonoxybenzalphenylhydrazone and *p-n*-Decyloxybenzalphenylhydrazone

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It is well known that a large number of organic compounds are mesomorphic in character. Even though it is not the purpose of this report to emphasize that the phenylhydrazones described here are mesomorphic, it might be mentioned that no phenylhydrazones with this property appear to have been described in the literature previously. An extensive review of the structure and the properties of the mesomorphic state may be found in a recent article by Brown and Shaw.[1]

Phototropic character of a number of both inorganic and organic compounds is also well established. Marckwald[2] gave the name "phototropy" to the phenomenon in which a solid changes color when exposed to light but reverts to its original color in the dark. Chalkley[3] reviewed the subject of phototropy a number of years ago. A number of phenylhydrazones have been described in the literature as phototropic and those described before 1928 are cited in Chalkley's review.[3] Gheorghiu and Matei[4] found the α-phenylhydrazones of 1-benzylidene-2-propanone, 1-benzylidene-2-pentanone, and 4-methyl-1-piperonylidene-2-pentanone are all phototropic but these compounds were not described as mesomorphic in character. Matei[5] reported the phototropic character of the α-phenylhydrazones of 1-benzylidene-2-butanone and of 1-benzylidene-2-pentanone but they were not described as showing mesomorphism.

The purpose of this preliminary report is to record two compounds which exhibit the properties of both mesomorphism and phototropism. No such compounds appear to have been described in the literature previously.

In the progress of research on the mesomorphic properties of a series of phenylhydrazones, it was found that *p-n*-nonoxybenzalhydrazone and *p-n*-decyloxybenzalphenylhydrazone both exhibit phototropy and mesomorphism. *p-n*-Nonoxybenzalphenylhydrazone has a crystalline-nematic point of 94–95° and a nematic-liquid point at 97–98°. It gives white flakes on crystallization from ethanol; these white flakes turn pink on exposure to direct sunlight. The compound was recrystallized from ethanol until it showed constant transition points.

Anal. Calcd. for $C_{22}H_{30}ON_2$: C, 78.06; H, 8.93. Found: C, 77.86; H, 8.72.

The color change from white to pink is rapid, taking place in less than five minutes. The reverse process, pink to white, takes place in about two hours. *p-n*-Decyloxybenzalphenylhydrazone crystallizes from ethanol to give white flakes which turn red on exposure to sunlight; the reverse process also takes place but is much slower than the rate of excitation. The time change on color transitions for this compound are comparable to those of *p-n*-nonoxybenzalphenylhydrazone. *p-n*-Decyloxybenzalphenylhydrazone has a crystalline-nematic point of 91–92° and a nematic-liquid point of 93–94°. The compound was recrystallized from ethanol until it showed constant transition points.

Anal. Calcd. for $C_{23}H_{32}ON_2$: C, 78.36, H, 9.15. Found: C, 78.11; H, 9.02.

The phototropic process for both compounds can be repeated again and again. No study has been made whether or not the compounds fatigue.

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Action of Grignard Reagents on Triphenylacetyl Chloride

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In an attempt to prepare methyl trityl ketone by the addition of methylmagnesium iodide to

triphenylacetyl chloride a 67% yield of *ethyl* triphenylacetate was obtained. The ester was identified by analysis and a comparison of the infrared spectrum with that of a sample synthesized from the acyl halide and ethanol. The probable route for the formation of this product is by cleavage of the solvent, ethyl ether, by the acyl chloride in the presence of magnesium iodide or other Lewis-acid component of the Grignard reagent. Cleavage of ether as a minor side reaction in the Grignard process has been reported previously. Small amounts of ethyl *t*-butylacetate were isolated when *t*-butylacetyl chloride was treated with several Grignard reagents.[2] Furthermore, anhydrous magnesium chloride was shown to catalyze the cleavage of ethyl ether by acetyl chloride.[3]

$$Ph_3CCOX \xrightarrow{MX_2} Ph_3\dot{C}\dot{C}O\ MX_3^- \xrightarrow{Et_2O}$$

$$Ph_3CC(=O)\overset{+}{O}(Et)\ MX_3^- \longrightarrow Ph_3CCO_2Et + EtX + MX_2$$

The lack of addition by the simplest Grignard reagent and the large amount of ether cleavage by triphenylacetyl chloride was not consistent with the reported preparation of ethyl trityl ketone from this acyl halide and ethylmagnesium iodide.[4] Consequently, this earlier preparation was repeated exactly as described except that the entire product was extracted into carbon tetrachloride for infrared analysis. No carbonyl compounds were present. Instead, the spectrum showed a strong, sharp peak at 2.83 μ characteristic of the hydroxyl group. The product melting at 103–105°, previously called triphenylmethyl ethyl ketone,[4] was identified as 2,2,2-triphenylethanol, identical to that synthesized from sodium triphenylmethide and formaldehyde. This product is formed by the well known reducing action of Grignard reagents containing β-hydrogen atoms.

$$Ph_3CCOCl + C_2H_5MgBr \longrightarrow Ph_3CCHO + C_2H_4 + MgBrCl$$

$$PH_3CCHO + C_2H_5MgBr \longrightarrow Ph_3CCH_2OMgBr + C_2H_4$$

When ethylmagnesium bromide is added to the aliphatic analog, trimethylacetyl chloride, the products are trimethylacetaldehyde (2%), ethyl *t*-butyl ketone (5.5%), neopentyl alcohol (15%) and ethyl-*t*-butylcarbinol (56%). However, in this case, the alcohols are isolated as their trimethylacetates.[5] Both this fact and the formation of ketone illustrate the greater reactivity of the carbonyl group in trimethylacetyl chloride than that in the aromatic acyl halide. Steric hindrance is probably responsible for this difference, for polar factors should increase the electrophilicity of the carbonyl group in triphenylacetyl chloride. To date, no alkyl trityl ketones have been made by the Grignard reaction; in fact, methyl trityl ketone, prepared by the dehydration and rearrangement of 1,1,2-triphenyl-1,2-propanediol,[6] is the only known member of this series.

EXPERIMENTAL

Triphenylacetic acid. A saturated solution of chlorotriphenylmethane, 118 g., 0.425 mole, in 800 ml. of dry ether was added slowly with stirring to an ice cold mixture of 30 g., 1.25 moles, of powdered magnesium, iodine catalyst, and 900 ml. of anhydrous ether. Reaction began immediately. Gentle reflux was maintained during the addition and for 4.5 hr. thereafter. A white solid precipitated during this time. Carbon dioxide gas was bubbled into the mixture until the precipitate dissolved. Hydrolysis by cold dilute hydrochloric acid gave 120 g. (98.5%) of triphenylacetic acid, m.p. 264–265° with decomposition. Recrystallization from 95% ethanol gave material melting at 269–270° without decomposition. The highest m.p. recorded for this compound is 271°.[7] The formation of triphenylmethylmagnesium chloride is highly exothermic. A violent reaction resulting in loss of material occurred when the halide was added in one portion.[8]

Triphenylacetyl chloride. Triphenylacetic acid, 6.4 g., 0.022 mole, was refluxed for 4.5 hr. with 25 ml. of purified thionyl chloride.[9] When cool, the mixture was poured into 75 ml. of 95% ethanol. Much gas was evolved, and white crystalline triphenylacetyl chloride was precipitated; m.p. 127–128° with no decomposition up to 134°. Although the yield was only 2.0 g. (34%), the product was much better than that obtained when the reaction mixture was poured onto ice and the resulting solid recrystallized twice from chloroform. This material melted at 126–127° with evolution of gas. The best m.p. recorded for this compound is 128–129° with decomposition.[10]

In two other preparations, the hot solution was poured into four times its volume of glacial acetic acid. After vigorous evolution of gases, the product crystallized slowly at 0°. Yields of 52 and 54% were obtained with melting points at 127–128° and 125–127°, the latter with evolution of gas.

Reaction of triphenylacetyl chloride and methyl Grignard reagent. To the Grignard solution prepared from 2.3 g., 0.096 mole, of magnesium, 16.0 g., 0.11 mole, of methyl iodide and 100 ml. of dry ether was added 1.7 g., 0.006 mole, of triphenylacetyl chloride. The solution was refluxed for 19

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hr. and poured with stirring into a 1:1 mixture of ice and concentrated hydrochloric acid. An ethereal solution of the product was washed with water and dried over calcium sulfate to give 1.26 g. (67%) of white solid, m.p. 110–115°. The solid was dissolved in cyclohexane and chromatographed on a 1 × 20 cm. column of Mallinckrodt analytical grade activated silica gel. Development and elution with cyclohexane gave 0.76 g., m.p. 115.8–116.4° from cyclohexane; 116.8–117.8° from methanol. The infrared spectrum in carbon tetrachloride and in a potassium bromide pellet exhibited a carbonyl peak at 5.77 μ. These constants did not correspond to those of methyl trityl ketone, m.p. 138°, C=O absorption maximum at 5.84 μ. Ethyl triphenylacetate has been reported to melt at 116–117°[11] and at 120–121°.[10] The above product was recovered unchanged after 13 hr. reflux with 10% sodium hydroxide solution; however, esters of triphenylacetic acid saponify with difficulty.[10]

Ethyl triphenylacetate was prepared by heating for one hour 2.56 g. of triphenylacetic acid in 15 ml. of purified[9] thionyl chloride, then refluxing the acyl halide for 21.5 hr. with 5 ml. of absolute ethanol. The product was treated with hot alcoholic potassium hydroxide to remove any excess acyl halide, and poured into water. The solid ester, obtained by extraction into ether and crystallization from 95% ethanol, melted at 115–116.5°. A carbon tetrachloride solution of the ester was chromatographed on a 1 × 20 cm. column of silica gel to give a product melting at 116–117° after recrystallization from methanol. The infrared spectrum of this material was identical with that from the reaction of triphenylacetyl chloride and methylmagnesium iodide in ethyl ether.

Anal. Calcd. for $C_{22}H_{20}O_2$: C, 83.54; H, 6.33. Found: C, 83.86; H, 6.40.

Reduction of triphenylacetyl chloride by ethylmagnesium iodide. To 5.0 g., 0.017 mole, of acyl halide in 50 ml. of dry ether was added slowly 60 ml. of 1.4 M ethylmagnesium iodide. Heat and gas were evolved. The gas was collected in a trap cooled by liquid nitrogen and was later expanded at 25° into a 1160-ml. storage system. The final pressure in the system was 424 mm. The infrared spectrum was identical to that of pure ethylene except for a small peak at 8.8 μ which was probably due to ether vapor. Comparison of the absorbancy at 10.98 μ with that of a sample of Matheson C.P. ethylene showed that the gas was 96.5% ethylene. The amount corresponds to 0.026 mole or 76% based on the reduction of the acyl halide through the aldehyde to the primary carbinol.

The residue was hydrolyzed by the addition of 35 ml. of water and 25 ml. of hydrochloric acid. The water layer was extracted with four 20-ml. portions of carbon tetrachloride and concentrated by fractionation through a 12-plate column. The residue from the distillation was made up to 50.0 ml. with carbon tetrachloride. The infrared spectrum contained a strong, sharp OH peak at 2.83 μ and no absorption in the carbonyl region. The solution was washed with sodium thiosulfate, concentrated to 15 ml., diluted hot with an equal volume of ethanol and cooled to 0°. Crystals weighing 1.8 g. were isolated and recrystallized six times from hexane to give 2,2,2-triphenylethanol, m.p. 103–105°.[12]

Anal. Calcd. for $C_{20}H_{18}O$: C, 87.59; H, 6.57. Found: C, 87.29; H, 6.41.

A sample of the carbinol was converted to the acetate, m.p. 135–137°; reported m.p. 136°.[13] The absorbance of the carbinol at 9.43 μ obeyed Beer's law and was used to estimate the total yield of carbinol in the original carbon tetrachloride extract. This amount, 1.3 g., represents a yield of 30% of the primary alcohol. The OH peak at 2.83 μ, however, was larger than that calculated from this amount of carbinol and indicates the presence of another more soluble alcohol in the mother liquors. One possibility is ethyltritylcarbinol from the addition of ethylmagnesium iodide to the intermediate triphenylacetaldehyde.

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Improved Procedure for Condensation of Alkyl Azides with Phenylacetonitrile to Form *vic*-Triazoles

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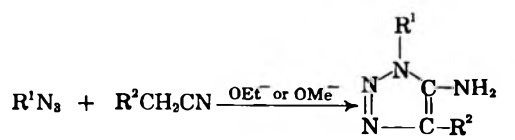
The elegant method for the synthesis of 1,4-disubstituted-5-amino-1,2,3-triazoles, III, first described by Dimroth,[2] involving the reaction of an organic azide, I, with an acetonitrile, II, in the presence of stoichiometric quantities of sodium ethoxide gives excellent yields for those cases in which the R substituent of I is an aromatic ring.[3] The yields were found to be poor when the benzyl



I II III ($R^2 = C_6H_5$)

and alkyl azides were employed. In the case of benzyl azide long periods of heating were required to effect condensation; even greater difficulties were experienced for alkyl azides in which R^1 was C_2H_5 and n-C_6H_{13}. Only in the case of ethyl azide was it possible to obtain a small quantity of the expected triazole; the major product when R^1 was C_2H_5 and n-C_6H_{13} consisted of an unknown substances[3a] whose elemental composition corresponded to the addition of two moles of II (R^2 = C_6H_5) and one mole of I (R^1 = C_2H_5 and n-C_6H_{13}). This communication reports on a significant improvement in the synthesis of III (R^1 = $C_6H_5CH_2$) and a new triazole, R^1 = n-C_6H_{13}, hitherto unattainable by the previous procedures.[3]

When n-hexyl azide was stirred at room temperature with II (R^2 = C_6H_5) in anhydrous tetrahydrofuran (THF) as solvent in the presence of an equimolar amount of potassium *tert*-butoxide (KTB), a practically quantitative yield of III (R^1 = n-C_6H_{13}) was obtained. Previous experiments[3a] using benzyl azide gave a 59% yield of a very impure and difficultly purifiable III (R^1 = $C_6H_5CH_2$)

(1) To whom all correspondence should be addressed.

(2) O. Dimroth, *Ber.*, **35**, 1034 (1902).

(3) (a) E. Lieber, T. S. Chao, and C. N. R. Rao, *J. Org. Chem.*, **22**, 654 (1957); (b) E. Lieber, T. S. Chao, and C. N. R. Rao, *Org. Syntheses*, **37**, 26 (1957).

after a reaction time of *ninety hours* at 60–65°. Repetition of this experiment in THF using KTB at *room temperature* for twelve hours gave a 78% yield of a 1:1 condensation product readily yielding pure III ($R^1 = C_6H_5CH_2$) identical with the product previously reported.[3a]

EXPERIMENTAL

Melting points are uncorrected. Micro-analyses by Dr. C. Weiler and Dr. F. B. Straus, Oxford, England.

1-n-Hexyl-4-phenyl-5-amino-1,2,3-triazole. To a mixture comprising 1.27 g. (0.01 mole) of *n*-hexyl azide,[3a] 1.17 g. (0.01 mole) of phenylacetonitrile in 50 ml. of dry THF was added a solution of 1.12 g. (0.01 mole) of KTB (dissolved in 50 ml. of THF) over a period of 30 min. The mixture was stirred at room temperature for a period of 12 hr. and then poured into ice water (400 ml.). The precipitated yellow crystals were filtered and vacuum dried; 2.3 g. (98%); m.p. 79–81°. Recrystallization from benzene gave m.p. 87–88°.

Anal. Calcd. for $C_{14}H_{20}N_4$: C, 68.82; H, 8.25; N, 22.93. Found: C, 68.57; H, 8.46; N, 23.10.

1-Benzyl-4-phenyl-5-amino-1,2,3-triazole. The reaction mixture comprised 5.85 g. (0.05 mole) of phenylacetonitrile, 6.65 g. (0.05 mole) of benzyl azide,[3a] and 5.6 g. (0.05 mole) of KTB in a total volume of 200 ml. of THF. The procedure used above was followed yielding 9.5 g. (78%) of the desired compound which on recrystallization melted at 156–156.5°. Mixture melting point with an authentic specimen[3a] showed no depression.

Acknowledgment. The authors gratefully acknowledge the receipt of research grants from the Eli Lilly Company, Indianapolis, Ind., and the Research Corporation, New York, N. Y., which made this study possible.

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Reaction of Primary Aliphatic Amines with Maleic Anhydride

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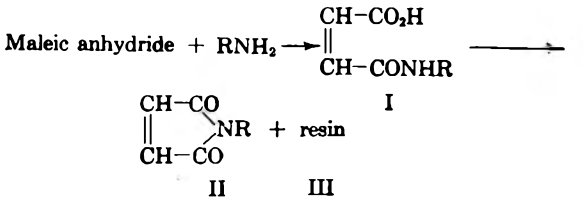
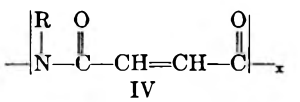
Received August 26, 1958

The reaction of primary amines with maleic anhydride has been known for many years[1]; however, with the exception of methyl and ethylamine,[2] the use of aliphatic primary amines has been reported only recently in the patent literature.[3,4] The reactions described in these patents are incomplete in nature and the products are not characterized. The reaction proceeds through the maleamic acid (I) intermediate to the maleimide (II) and a resinous by-product (III) as shown in the equation:



We have prepared a series of seven maleamic acids by reacting maleic anhydride with the appropriate amine in toluene at 90°. Amines containing from 4 to 18 carbon atoms were used. The acids were isolated in good yields as white crystalline solids.

Four *N*-alkyl maleimides were prepared by reacting maleic anhydride with the appropriate amine in xylene at 170–180°. The maleimides could also be prepared under the same conditions by starting with the *N*-alkyl maleamic acid. Low yields of product were obtained due to a concurrent polymerization reaction. The preparation of *N*-butyl maleimide was studied more extensively than the others. Yields of product were increased to 50% by removing solvent and then product and water under vacuum. In attempts to reduce the polymer formed in this reaction, hydroquinone and *p-t*-butylcatechol were added as inhibitors but were ineffective, suggesting that the reaction is not catalyzed by free radicals. The polymer appears to be a condensation product of the *N*-alkyl maleamic acid intermediate with the structure IV.



The infrared spectrum of IV showed the presence of unsaturation and differed from a spectrum of a free radical-catalyzed homopolymer of *N*-butyl maleimide which showed no unsaturation.

The *N*-alkyl maleamic acids and the corresponding maleimides have been investigated as monomers and details will be reported elsewhere.

EXPERIMENTAL[5]

Maleamic acids. General procedure: Maleic anhydride (0.5 mole) and 100 g. toluene were mixed at 90°. The appropriate amine (or Armeen[6]) (0.5 mole) was added slowly over a 2-hour period and the mixture was heated an additional hour at 90°. The mixture was cooled and the product was filtered. After washing with benzene and naphtha, the product was dried and then recrystallized from methanol-water as white crystals. The products are characterized in Table I.

Maleimides. Maleic anhydride and xylene were mixed at 80° and the appropriate amine was added at 80–90°. Equimolar amounts were used. Xylene was stripped off until the reaction temperature reached 180°, and the mixture was

(1) R. Anschütz, *Ber.*, 20, 3214 (1887).

(2) A. Piutti and E. Giustiniani, *Gazz. chim. ital.*, 26, I, 431 (1896).

(3) J. M. Weiss and R. P. Weiss, U.S. Patent 2,306,918 (December 29, 1942).

(4) J. J. Giammaria, U.S. Patent 2,727,862 (December 20, 1955).

(5) All melting and boiling points are uncorrected.

(6) "Armeen" is the trade name for the primary aliphatic amines marketed by Armour and Co. The distilled samples were used in this study.

TABLE I

N-ALKYL MALEAMIC ACIDS

Alkyl Group	Yield, %	M.P., °C.	% N Theory	% N Found
Butyl	97.5	79–80	8.19	8.20
Octyl	63.4	80–82	6.18	6.08
Decyl	83.5	83–84	5.49	5.27
Dodecyl	72	92–94	4.95	5.01
Tetradecyl	55	96–97.5	4.50	4.51
Hexadecyl	77.5	99–101	4.13	4.29
Octadecyl	86	102–104	3.81	3.87

held at this temperature for 2 hr. The residue was heated under reduced pressure and the water and product distilled off to a pot temperature of 210°/30 mm. The crude product was then redistilled under reduced pressure. The maleimides are characterized in Table II. The synthesis of *N*-butyl maleimide was improved by removing the xylene under reduced pressure. Yields of 50% were obtained.

TABLE II

N-ALKYL MALEIMIDES

Alkyl Group	Yield, %	M.P., °C.	% N Theory	% N Found
Butyl	25	103–104[a]	9.15	9.04
Octyl	15	37–37.5	6.70	6.74
Decyl	20	46.5–48	5.91	6.01
Dodecyl	24	54.5–56.0	5.29	4.99

[a] B.p. at 20 mm. Hg.

Acknowledgment. The authors wish to thank H. Ferber and R. Andrassy for the nitrogen analyses and Miss F. Judnick for the infrared spectra.

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Reaction of Methylene with Diethyl Ether and Tetrahydrofuran

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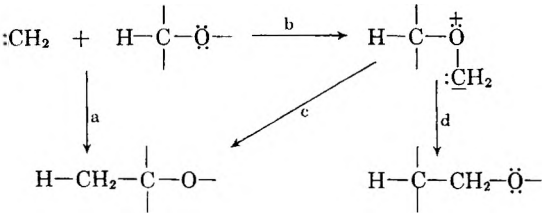
Received September 2, 1958

In their pioneer study of the photochemically induced reaction of methylene with organic molecules, Meerwein, Rathjen, and Werner[1] discovered that diethyl ether gave ethyl *n*-propyl and *i*-propyl ethers and that tetrahydrofuran gave α- and β-methyltetrahydrofuran. Here was the first example of the insertion of methylene into the carbon hydrogen bond. Later, this reaction was extended to saturated hydrocarbons by Doering, Buttery, Laughlin, and Chaudhuri.[2] In these instances methylene reacted indiscriminately with the various kinds of hydrogen atom. We wondered whether ether oxygen would permit the operation of the "ylid" mechanism discussed by Huisgen[3] (Chart 1, paths b and c) and thus cause the ratio of products to deviate from the statistical expected of the direct insertion mechanism (Chart 1, path a).

In the reaction with cyclopentane[2] participation of a direct insertion into the carbon-carbon bond, to form cyclohexane, was not observable. With ethers, however, intermediate "ylid" formation might be followed by rearrangement (Chart 1, paths b and d), with insertion into the carbon-carbon bond being the end result. As first pointed



out by Gutsche and Hillman, tetrahydrofuran is an apt substrate for examination of this possibility.[4]

This note is, accordingly, concerned with the repetition of the Meerwein studies with the use of gas-liquid partition chromatography as a more refined analytical method than any conveniently available at the time of Meerwein's work.

The experiments were carried out in the usual way, by preparing a solution of diazomethane in a large excess of the substrate and irradiating with light of wave lengths greater than *ca.* 300 mμ. The bulk of the solvent was removed by distillation through a fractionating column. The concentrate of the product was analyzed by g. l.p.c. Retention times and sensitivities were determined on synthetic samples; identification was effected by comparison of infrared spectra.

From diethyl ether, ethyl *n*-propyl ether and ethyl *i*-propyl ether were obtained in the ratio 55.5 to 44.5. The deviation from the statistical value, 60:40 is small. The ratio of reaction of α-hydrogen to β- is 1.23. The ratio predicted on the basis of indiscriminate reaction of methylene is, of course, 1.00.

Tetrahydrofuran afforded α- and β-methyltetrahydrofuran in the ratio 1.26, in contrast again to the predicted value of 1.00. No tetrahydropyran could be found among the products. Especial care was exercised so that quite small amounts could have been detected. By the method described in the EXPERIMENTAL, 0.5% would have been detected easily, whereas the detection of 0.1% or less would have been equivocal. Reaction with the carbon-oxygen bond (or with the carbon-carbon bond) does not occur within these experimental

(1) H. Meerwein, H. Rathjen, and H. Werner, *Ber.*, **75**, 1610 (1942).

(2) W. von E. Doering, R. G. Buttery, R. G. Laughlin, and N. Chaudhuri, *J. Am. Chem. Soc.* **78**, 3224 (1956).

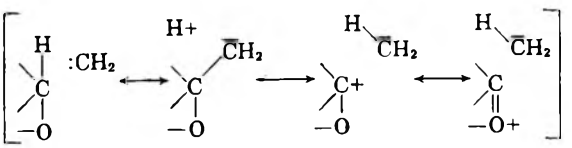
(3) R. Huisgen, *Angew. Chem.*, **67**, 439 (1955).

(4) C. D. Gutsche and M. Hillman, *J. Am. Chem. Soc.*, **76**, 2236 (1954).

limits. Rearrangement of a hypothetically intermediate "ylid", urged so strongly by Meerwein and coworkers,[5] is therefore unimportant in the reaction of methylene with tetrahydrofuran and, presumably, with diethyl ether also.

The deviation from the statistical distribution in the reaction of methylene with the carbon-hydrogen bonds is small and lies in the direction of favoring the α-hydrogen atoms. Granting that the deviations are significant, one can rationalize their direction by comparing transition states of the type considered by Doering and Knox.[6] In the ethers, the transition state of reaction with the α-hydrogen could be favored by contribution of a resonance structure involving the oxygen atom.

It may be pointed out that appreciable carbon-rearrangement of the hypothetical diethyl ether–methylene "ylid" would have led to deviation in the opposite direction from that observed, whereas



hydrogen-rearrangement from such an "ylid" would have led to deviation in the observed direction.[7]

These quantitatively more reliable results in no way change those reported by Meerwein and co-workers.[1] The conclusions are perhaps best expressed in a negative way: There is no new phenomenon in the reaction of these two ethers with methylene to compel one to consider the possible intervention of an "ylid" intermediate. It should, however, be pointed out that there are far more compelling reasons to consider an intermediate "ylid" in reactions of ethyl diazoacetate.[4,5,8]

EXPERIMENTAL

Photochemical decomposition of diazomethane in diethyl ether. An ethereal solution of diazomethane was prepared from 105 g. of crude nitrosomethylurea and 11 g. of purified diethyl ether and dried over potassium hydroxide at 0°. Irradiation with two General Electric sunlamps at 15–17° caused the smooth evolution of nitrogen and complete decolorization of the solution in 18 hr. The bulk of the solvent was removed by distillation through a 2-ft. column packed with glass helices. Total distillation of the residue gave 18.1 g. of a colorless product of b.p. 50–72°. Analysis and separation by g.l.p.c. afforded diethyl ether, ethyl *i*-propyl ether, and ethyl *n*-propyl ether. The substances were identified by comparing the infrared spectra with those of authentic materials. The ratio of *n*-propyl to *i*-propyl ether, determined by area measurement and corrected for differences in sensitivity, was 1.25.

Authentic ethyl *n*-propyl ether was prepared from sodium propoxide and ethyl iodide in boiling propanol-1; b.p. 63–64°; n_D^{25} 1.3698. Ethyl *i*-propyl ether was prepared in a similar fashion: b.p. 53.5°; n_D^{25} 1.3624.

Photochemical decomposition of diazomethane in tetrahydrofuran. In the same manner as described above, the irradiation of diazomethane in tetrahydrofuran (purified by boiling under reflux over sodium and distilling) gave 30.2 g. of crude product; b.p. 85–115°. Separation by g.l.p.c. showed recovered tetrahydrofuran, 2-methyltetrahydrofuran, and 3-methyltetrahydrofuran. The ratio of the latter compounds was 1.26. Identification was by comparison of infrared spectra with those of authentic materials.

Samples of tetrahydropyran (b.p. 86°; n_D^{25} 1.4206) and 2-methyltetrahydrofuran (b.p. 80°; n_D^{25} 1.4052) were obtained commercially and refractionated. 3-Methyltetrahydrofuran was obtained by the sequence of reactions in which methylsuccinic acid was converted to the dimethyl ester, b.p. 195–197.5°, by ethereal diazomethane; the diester was reduced with lithium aluminum hydride to 2-methylbutandiol-1,4, b.p. 95–97°/1 mm.; and the diol was treated with 60% sulfuric acid in a sealed tube at 100° according to Yur'ev and Gragerov.[9] A pure sample isolated by g.l.p.c. had b.p. 85–87° (reported[8] 86–86.5°) and n_D^{25} 1.4012.

The question of the possible presence of tetrahydropyran was examined. The retention time of authentic tetrahydropyran is slightly longer than that of 3-methyltetrahydrofuran on a column of dioctylphthalate under the conditions we used. No peak or shoulder at this retention time was observed. To eliminate the possibility of smaller amounts having been formed, 3 cc. of the crude reaction product (containing about 10% tetrahydrofuran) was separated on a 5-ft., 2″ I.D., silicone-firebrick column into starting material, 2-methyltetrahydrofuran and 3-methyltetrahydrofuran. The last quarter of the 3-methyltetrahydrofuran peak was collected and its infrared spectrum was measured neat in a 0.025 mm. cell. The strong absorption band of tetrahydropyran at 873 cm.$^{-1}$ is useful for detecting small amounts of this material. There is a slight discrepancy at this frequency corresponding to *ca.* 2%. When 0.011 g. of tetrahydropyran was added to 1.1 g. of the reaction product (bulk of tetrahydrofuran removed) the band was easily identifiable in the final quarter of the 3-methyltetrahydrofuran band and corresponded in intensity to about 6%.

HICKRILL CHEMICAL RESEARCH FOUNDATION
KATONAH, N. Y.

(5) H. Meerwein, H. Disselnkötter, F. Rappen, H. v. Rinteln, and H. van de Vloed, *Ann.*, **604**, 151 (1957).

(6) W. von E. Doering and L. H. Knox, *J. Am. Chem. Soc.*, **78**, 4947 (1956).

(7) Assuming that all hydrogen atoms react indiscriminately and that the "ylid" rearranges only to the α-methyl homologue, the reactivity of the oxygen atom towards methylene, relative to hydrogen taken as 1.00, becomes 1.04.

(8) G. B. R. de Graaff, J. U. Van Dijck-Rothuis, and G. van de Kolk, *Rec. trav. chim.*, **74**, 143 (1955).

(9) Yu. K. Yur'ev and I. P. Gragerov, *Zhur. Obschei* (*J. Gen. Chem.*) **18**, 1811 (1948); *Chem. Abstr.*, **43**, 3818 (19

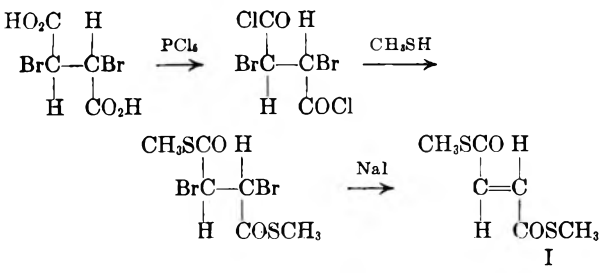
Dimethyl Dithiolfumarate and Some Copolymerization Reactions[1]

C. S. MARVEL AND J. F. PORTER

Received September 24, 1958

Dimethyl dithiolfumarate (I) has been prepared from fumaric acid by the following series of reactions:

(1) This is a partial report of work done under contract with three Utilization Research and Development Divisions, Agricultural Research Service, U. S. Department of Agriculture, and authorized by the Research and Marketing Act. The contract was supervised by Dr. J. C. Cowan of the Northern Division.



The method used and the various steps are analogous to those used for making dialkyl thiolacrylate esters.[2]

Dimethyl dithiolfumarate could not be homopolymerized, but it does copolymerize with styrene and butadiene. No copolymerization with vinyl chloride could be achieved. The copolymerization of the dithiol ester with butadiene in the Mutual recipe[3] proceeded readily and with a charge ratio of 1 part of butadiene and 9 parts of dithiol ester, copolymer containing 7 parts of butadiene to 3 parts of dithiol ester was obtained.

Reactivity ratios were determined between the dithiol ester and butadiene and styrene using the standard procedures.[4] For dimethyl dithiolfumarate and butadiene, the values are $r_1 = -0.0014 \pm 0.027$ and $r_2 = 0.0106 \pm 0.0175$, respectively. For the dithiol ester and styrene, the values are $r_1 = 0.0163 \pm 0.013$ and $r_2 = 0.098 \pm 0.013$, respectively. It may be noted that the reactivity ratios for diethyl fumarate and styrene are $r_1 = 0.025 \pm 0.015$ and $r_2 = 0.21 \pm 0.02$[5] and for diethyl fumarate and butadiene are $r_1 = 0.25$ and $r_2 = 2.13$,[6] respectively.

EXPERIMENTAL

α,α'-Dibromosuccinyl chloride was prepared by adding bromine to sodium fumarate, converting the dibromo salt to the free acid and treatment of this with phosphorus pentachloride as described by Lutz.[7]

Dimethyl α,α'-dibromodithiolsuccinate. In a half-liter, three-necked, round-bottomed flask were placed 24 g. (0.5 mole) of methanethiol. To avoid the loss of the volatile mercaptan the flask was cooled in an ice bath and fitted with a condenser containing Dry Ice and acetone. Seventy grams (0.224 mole) of α,α'-dibromosuccinyl chloride was added dropwise to the thiol. When hydrogen chloride was no longer liberated, the reaction mixture was dissolved in ether and the solid was purified by three successive crystallizations from ether. Yield: 42 g. (56% based on the acid chloride), m.p. 171–172°.

Anal. Calcd.: C, 21.4; H, 2.3; Br, 47.6; S, 19.0. Found: C, 22.22; H, 2.70; Br, 43.68; S, 19.78.

Dimethyl dithiolfumarate. A solution of 20.3 g. of dimethyl α,α'-dibromodithiolsuccinate dissolved in 400 ml. of acetone was prepared. A second solution of 25 g. of sodium iodide dissolved in 300 ml. of acetone was placed in a one-liter, three-necked flask fitted with a stirrer, reflux condenser, and dropping funnel. The stirrer was started, the first solution was added dropwise to the flask, and the mixture stirred for 4 hr. after the addition was complete. The precipitated sodium bromide was removed by filtration and the solution was concentrated on a steam bath to about one third of the original volume. Five hundred milliliters of ether was then added, and the mixture was washed with a 10% aqueous solution of sodium thiosulfate until all the color due to free iodine was removed. The ether was removed by distillation on a steam bath at atmospheric pressure until the first crystals appeared in the ethereal solution. The solution was allowed to cool to room temperature and then cooled in a Dry Ice–acetone bath. The unsaturated ester was removed by filtration and recrystallized from ether. Yield: 45%, m.p. 78–79°.

Anal. Calcd.: C, 40.9· H, 4.55; S, 35.9. Found: C, 40.61; H, 4.74; S, 36.04.

Dimethyl dithiolfumarate–butadiene copolymer. In a standard emulsion system a charge of 17.5 g. of 2.86% ORR soap solution in redistilled water, 0.024 g. of Hooker's lauryl mercaptan, 1.0 g. of butadiene, 9.0 g. of dimethyl dithiolfumarate, and 1 ml. of a 3% aqueous solution of potassium persulfate was used in the usual 4-oz. screw-cap polymerization bottle. Polymerization was allowed to proceed at 50° for 5 hr. with end-over-end agitation. The polymer was coagulated in the usual manner, washed thoroughly, dissolved in benzene, and reprecipitated by pouring into methanol. This was repeated three times. The polymer was then dried. Four runs gave yields of about 1.2–1.3 g. The inherent viscosities varied from 2.13–2.24 (0.25 g./100 ml. benzene at 25°).

Anal. Found: C, 74.03; H, 8.92; S, 12.17.

This corresponds to a ratio of 7 parts of butadiene to 3 parts of dimethyl dithiolfumarate in the copolymer.

Reactivity ratios. The method of Mayo and Lewis[4] was followed. Benzene was used as the solvent and benzoyl peroxide as the initiator. Conversion was less than 5% in every case. The experimental data for the reactivity ratios of the ester with butadiene is given in Table I and with styrene in Table II.

TABLE I

DATA USED IN CALCULATION OF REACTIVITY RATIOS OF STYRENE AND DIMETHYL DITHIOLFUMARATE

Sample	Charge: Dimethyl dithiolfumarate, g.	Charge: Styrene, g.	M_1^a/M_2	Product: % S	Product: % C	Product: m_2^b/m_1
1	0.2222	1.7371	0.0755	15.30		2.3332
2	0.2335	3.5551	0.04102	12.40		3.2747
3	3.8237	2.3573	0.9585		60.86	1.0756
4	3.9069	0.8510	2.7133		60.29	1.0274
5	1.1866	2.5638	0.2735		63.92	1.3758
6	4.2684	0.8981	2.8074		60.06	1.0080

[a] $\frac{M_1}{M_2}$ = mole ratio, dimethyl dithiolfumarate/styrene in the charge. [b] $\frac{m_2}{m_1}$ = mole ratio, styrene/dimethyl dithiolfumarate in the product.

(2) C. S. Marvel, S. L. Jacobs, W. K. Taft, and B. G. Labbe, *J. Polymer Sci.*, **19**, 59 (1956).

(3) R. L. Frank, C. E. Adams, J. R. Blegen, R. Deanin, and P. V. Smith, *Ind. Eng. Chem.*, **39**, 887 (1947).

(4) F. R. Mayo and F. M. Lewis, *J. Am. Chem. Soc.*, **66**, 1594 (1944).

(5) F. M. Lewis, C. Walling, W. Cumings, E. R. Briggs, and F. R. Mayo, *J. Am. Chem. Soc.*, **70**, 1519 (1948).

(6) M. F. Margaritova and G. D. Bereyhnai, *Trudy Muskov. Inst. Tonkoĭ Khim. Tekhnol.*, **1953**, No. 46 [*Chem. Abstr.*, **50**, 1361 (1956)].

(7) R. E. Lutz, *J. Am. Chem. Soc.*, **49**, 1106 (1927).

TABLE II

DATA USED FOR THE CALCULATION OF REACTIVITY RATIOS OF DIMETHYL DITHIOLFUMARATE AND BUTADIENE

Sample	Charge: Dimethyl dithiolfumarate, g.	Charge: Butadiene, g.	M_1^a/M_2	Product: % C	Product: m_2^b/m_1
1	1.2695	1.2598	0.3092	52.47	1.0387
2	1.1694	0.7241	0.4950	53.03	1.0610
3	1.3908	0.8747	0.4879	52.31	1.0199
4	1.484[illegible]	0.1954	2.3308	52.18	1.0058
5	1.0563	0.4652	0.6968	52.04	1.9885

[a] $\frac{M_1}{M_2}$ = mole ratio, dimethyl dithiolfumarate/butadiene in the charge. [b] $\frac{m_2}{m_1}$ = mole ratio, butadiene/dimethyl dithiolfumarate in the product.

The data thus obtained were plotted and calculated in the usual manner.

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Reaction of Dichlorocarbene with Conjugated Dienes[1]

MILTON ORCHIN[2] AND E. C. HERRICK[3]

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A recent article[4] describing the addition of dihalocarbenes to 1,3-butadiene prompts us to report similar work which has been in progress for several years. Our results corroborate the published work; addition to butadiene occurs almost exclusively at the 1,2-position. In addition to the expected 1,1-dichloro-2-vinylcyclopropane, a compound with properties consistent with the structure of 2,2,2′,2′-tetrachlorobicyclopropyl was isolated; its formation can be explained by 1,2- and 3,4- double addition of the dichlorocarbene.

We wish to report here in detail our experiments with isoprene. 1,2-Addition to this unsymmetrical diene could lead to two different products. Structural information was secured as follows: After treatment of the isoprene with chloroform in the presence of potassium isopropoxide, the product was dechlorinated with sodium in liquid ammonia containing methanol. The hydrocarbon mixture was recovered and saturated with hydrogen. Mass spectra analysis of the saturated hydrocarbons showed that the product was principally that resulting from 1,2-addition to the substituted double bond of isoprene; small amounts of material corresponding to addition at the other double and some evidence for 1,4-addition were also found, although evidence for the 1,4-addition was inconclusive.

EXPERIMENTAL[5]

Experiments with Butadiene. 2,2,2′,2′-Tetrachlorobicyclopropyl. Reaction of butadiene with chloroform in the presence of sodium *tert*-butoxide gave the known[4] 1,1-dichloro-2-vinylcyclopropane. After its removal by distillation, the residue was distilled *in vacuo* and a fraction b.p. 76° (6 mm.) was collected which on crystallization from pentane had m.p. 79.5–80.5°.

Anal. Calcd. for C_6H_6Cl: Cl, 64.5; C, 32.7; H, 2.7. Found: Cl, 64.1; C, 33.0; H, 2.6.

The infrared spectrum showed bands at 3430, 2940, 1049, 1011, and 986 cm^{-1}. Such bands are consistent with the presence of cyclopropyl groups.[6]

1,1-Dichloro-2-ethylcyclopropane. A solution of 0.553 g. of 1,1-dichloro-2-vinylcyclopropane in 15 ml. of cetane was treated with hydrogen at atmospheric pressure in the presence of a reduced platinum catalyst (Houdry Type 3). Absorption of 1.10 moles of hydrogen per mole of compound occurred rapidly. Careful fractionation gave a forerun and then the bulk of the material distilled at 121°. Chlorine analysis indicated impurities present. In subsequent work a substantial quantity of 1,1-dichloro-2-ethylcyclopropane was isolated from the carbene reaction using sodium *tert*-butoxide. Possibly some sodium failed to react with the alcohol and during the work-up, sodium reduction of a portion of the 1,1-dichloro-2-vinylcyclopropane occurred. Careful fractionation gave material, b.p. 120°, n_D^{20} 1.4497, d_4^{20} 1.1171.

Anal. Calcd. for $C_5H_8Cl_2$: Cl, 51.0; C, 43.2; H, 5.8. Found: Cl, 51.0; C, 42.9; H, 5.8.

Experiments with Isoprene. 1,1-Dichloro-2-methyl-2-vinylcyclopropane. After the addition of 50 g. (1.25 moles) of potassium to 600 ml. of isopropyl alcohol (distilled from sodium) and complete disappearance of the potassium, the excess alcohol was removed by distillation. The potassium isopropoxide was dried overnight under reduced pressure at 100°. The salt was suspended in 200 ml. of petroleum ether and 150 ml. (1.5 moles) of isoprene (Philips Petroleum Company, 99%) was added. There was then added dropwise with stirring at 0°, about 150 g. (1.25 moles) of chloroform. There appeared to be an immediate reaction. The reaction mixture was stirred at 0° for 2 hr. after addition was complete, and the mixture was then poured into water. The organic phase was separated, washed with water, dried over anhydrous sodium sulfate, and the solvent was evaporated. The residue was distilled through a short helix-packed column to give two fractions the first of which was a forerun, 3.9 g., b.p. 60° (33 mm.). The second fraction had b.p. 64° (33 mm., 24.5 g.). This material reacted very slowly with potassium permanganate solution; there was almost no reaction with bromine water.

Anal. Calcd. for $C_6H_8Cl_2$: Cl, 46.9, M_D calcd. 37.4 (including the value 0.6 for the cyclopropane ring[7]). Found: Cl, 46.5; M_D, 37.8.

The infrared spectrum gave strong bands at 2985, 1640, 1440, 1100, 1088, 1051, 1026, 994, and 950 $cm.^{-1}$.

The same reaction was repeated on a large scale in a 5-gal.,

(1) Presented before the Second Delaware Valley Meeting, ACS, February 5 1958.

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(4) R. C. Woodworth and P. S. Skell, *J. Am. Chem. Soc.*, **79**, 2542 (1957).

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glass-lined kettle using a high-dilution technique[8,9] in which isoprene was used as solvent. To 3 gal. of *tert*-butyl alcohol which had been distilled from sodium carbonate, there was added 9.1 gram atoms of sodium. After the sodium had reacted, the excess alcohol was removed and the residual butoxide was dried at 60° in vacuo. The salt was suspended in 7 liters of isoprene and 9 moles of chloroform was added during 5.5 hr. at a slurry temperature of about 0°. The reaction product was isolated in the usual manner and fractionally distilled. The fractions b.p. 145° and with a constant refractive index (n_D^{25} 1.4787) were combined. Vapor fractometer analysis indicated a purity of about 96%. The yield of pure 1,1-dichloro-2-methyl-2-vinylcyclopropane based on sodium was 37.2%.

1-Methyl-1-vinylcyclopropane. To a mixture of 15.1 g. (0.1 mole) of 1,1-dichloro-2-methyl-2-vinylcyclopropane in 50 ml. of methanol and 100 ml. of liquid ammonia there was added portionwise 9.4 g. (0.4 mole) of sodium. As soon as the first few pieces were added, sodium chloride began to precipitate. The sodium dissolved rapidly with a transient blue color. Gradually the rate of reaction of the sodium decreased and at the completion of the addition of the 9.4 g. of sodium, there appeared to be an excess of sodium present. The ammonia was allowed to evaporate at room temperature. Unfortunately, most of the hydrocarbon was lost during the spontaneous evaporation of the ammonia. About 10 ml. of methanol was added followed by sufficient water to dissolve the salts. The small hydrocarbon layer was separated, washed with water, and filtered through calcium chloride. The product (one gram) had n_D^{25} 1.432 and gave a positive test for unsaturation with bromine water. Mass spectrographic analysis indicated the presence of 1-methyl-1-vinylcyclopropane, contaminated with a small quantity of other material.

1-Methyl-1-ethylcyclopropane. To 0.7031 g. (0.0094 mole) of the above impure 1-methyl-1-vinylcyclopropane there was added about 50 ml. cetane and 0.5 g. Type III Houdry catalyst (Pt on Al_2O_3). The sample was hydrogenated at 26° and one atmosphere of hydrogen. The rate of hydrogen uptake was constant at 4.2 ml./min. until 220.7 ml. was absorbed, then decreased to 0.6 ml./5 min. The uptake of 220.7 ml. of hydrogen corresponds to 1.03 moles per mole of 1-methyl-1-vinylcyclopropane. The reduced product was distilled through a microcolumn and 0.5 g. of distillate collected. Mass spectrographic analysis indicated the following hydrocarbons were present in the mole percentages given:

Compound	Mole %
3-Methylpentane	11.3
2,2-Dimethylbutane	1.9
2-Methylpentane	4.7
2,3-Dimethylbutane	
1-Ethyl-1-methylcyclopropane	74.3
Isopropylcyclopropane	3.4
Methylcyclopentane	4.4

The presence of the last two compounds was inferred on the basis of an excess at mass 39 and deficiencies at 55, 69, and 84 after the other components had been accounted for. The evidence for 1,4-addition leading to methylcyclopentane must accordingly be considered inconclusive at the present time.

2,2-Dichloro-1-methylcyclopropane-1-carboxylic acid. To 10.8 g. (0.071 mole) of 1,1-dichloro-2-methyl-2-vinylcyclopropane in 100 ml. of acetone there was added 2 g. of sodium bicarbonate. The mixture was cooled to 0° and 39 g. of potassium permanganate was added with stirring over about 4 hr. The mixture was poured into a beaker, the acetone was allowed to evaporate, and the residue was treated with solid sodium bisulfite and dilute sulfuric acid until the mixture was colorless. The reaction mixture was extracted with ether, and the ether extract was shaken with sodium bicarbonate solution. The sodium bicarbonate solution was acidified with dilute hydrochloric acid. The acid mixture was extracted with ether, and the ether solution was dried and distilled at 1 mm. The product boiling at 110° (1 mm.) amounted to 6.0 g. and crystallized on standing, m.p. 61°. The crude product was recrystallized twice from pentane to give white clusters of crystals, m.p. 60–62°.

Anal. Calcd. for $C_5H_6O_2Cl_2$: Cl, 42.0. Neut. equiv. 169. Found: Cl, 41.7. Neut. equiv. 173.5.

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Communications TO THE EDITOR

A New Fructose Anhydride

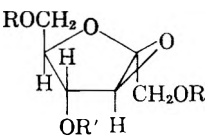
Sir:

Nitrates of ketohexoses, in contrast to aldohexoses, have not yet been obtained in the monomeric form. Schwager and Leibowitz[1] have recently shown that the nitration of fructose by means of a nitric-sulfuric acid mixture[2] affords a mixture of nitrates of difructose dianhydrides along with other dimeric derivatives of fructose. In a course of a study designed toward the formation of monomeric fructose nitrates we found that this could be achieved by using aprotic nitration agents.[3]

Nitration of fructose by means of N_2O_5 in chloroform according to the method of Caesar and Goldfrank[4] yielded a mixture of monomeric fructose nitrates. Fractional crystallization of this mixture afforded in 30% yield, long crystalline needles of a trinitrate (I), melting at 80.5° (from methanol). $[\alpha]_D^{25}$ = +34.5 (ethanol). *Anal.* Calcd. for $C_6H_7O_{11}N_3$: N, 14.14; mol. wt., 297. Found: N, 14.02; mol.wt., 300 (in benzene). In the infrared spectrum I shows three absorption bands at 1665 cm.$^{-1}$; 1306 cm.$^{-1}$ and 2180 cm.$^{-1}$ (O–NO_2). λ_{max}^{EtOH} 220 mμ, log ϵ, 3.28.

Catalytic reduction of I with palladium-charcoal (10%) in ethanol, according to Kuhn[5] resulted in complete denitrification, yielding a colorless sirup (II), $[\alpha]_D^{25}$ = +79.4 (ethanol). Infrared: 3366 cm.$^{-1}$, 3306 cm.$^{-1}$ (OH), 1064 cm.$^{-1}$ (C-O ethers) and 1263 cm.$^{-1}$ (epoxide). It did not respond to the Fehling test, but underwent facile acid hydrolysis in cold *N* hydrochloric acid solution affording fructose in quantitative yield, identified by its optical rotation, chromatographic R_f value and by its osazone (m.p. 207°). Acetylation of II by means of acetic anhydride–pyridine gave a crystalline triacetate (III), m.p. 112° (from ethanol), $[\alpha]_D^{25}$ = +57.4 (ethanol). *Anal.* Calcd. for $C_{12}H_{16}O_8$: C, 50.00, H, 5.59; mol. wt., 288. Found: C, 49.93, H, 5.1; mol. wt., 289. Infrared: 1751 cm.$^{-1}$ (C=O), 1230 cm.$^{-1}$ (C—O ether) 1264 cm.$^{-1}$ (epoxide). II resisted oxidation by means of potassium periodate even after prolonged standing. Exhaustive methylation of II followed by acid hydrolysis afforded a sirup which failed to produce an osazone. Tritylation of II by means of trityl chloride–pyridine[6] afforded a dityrityl derivative (IV) as colorless crystals (from ethanol) melting at 207°. *Anal.* Calcd. for $C_{44}H_{38}O_5$: C, 81.88; H, 5.88. Found: C, 81.74; H, 5.74. Infrared: 3410 cm.$^{-1}$, 3370 cm.$^{-1}$ (OH), 3030 cm.$^{-1}$ (C-H), 1262 cm.$^{-1}$ (epoxide). Tosylation of I by tosyl chloride–pyridine[7] gave exclusively a ditosyl derivative (V) as colorless crystals melting at 156° (from ethanol). *Anal.* Calcd. for $C_{20}H_{22}O_9S_2$: C, 51.48; H, 4.68; S, 12.86. Found: C, 51.52; H, 4.86, S, 12.5. Infrared: 3546 cm.$^{-1}$ (OH), 1373 cm.$^{-1}$, 1184 cm.$^{-1}$ (O–SO_2) 1265 cm.$^{-1}$ (epoxide). Heating a solution of V in acetone and sodium iodide at 100° produced two molar equivalents of sodium *p*-toluenesulfonate in quantitative yield along with an iodide derivative. Nitration of II by means of N_2O_5 in $CHCl_3$ resulted in the re-formation of I while nitration by means of HNO_3–H_2SO_4 caused polymerization.

The series of reactions clearly permits the assignment of 2,3-*anhydro*-fructofuranose structure for II. For absolute configuration assignment, we studied the mechanism of formation of I and the information now at hand suggests that the epoxide ring is oriented above the furanose ring,[3] as formulated below.



I. R=R'=No$_2$. II. R=R'=H. III. R=R'=Ac. IV. R=Tr; R'=H. V. R=Ts; R'=H.

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Azomethine and α-Bromoamine Formation in the Aralkylation of Certain Weak Aromatic Amines in Dimethyl Sulfoxide[1]

Sir:

Alkylation of weak aromatic amines with alkyl bromides (*e.g.*, 2-aminofluorenone with ethyl bro-

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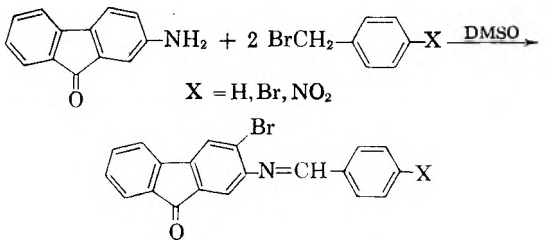
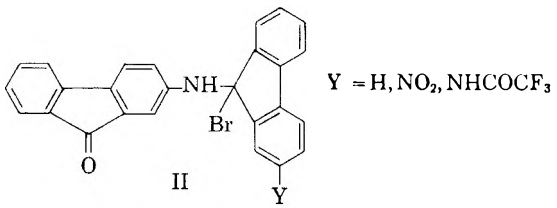
mide) in dimethyl sulfoxide gave ring brominated *N*-alkyl derivatives.[2] However, aralkylation of 2-aminofluorenone with aralkyl bromides, such as benzyl and *para* substituted benzyl bromides, in dimethyl sulfoxide (1.5 hours; 100°) leads to azomethines as main products (when X is Br or NO_2, the yield of I is 80%). The reaction of 2-



N-benzylaminofluorenones with 48% hydrobromic acid (2 equivalents) in dimethyl sulfoxide (1.5 hours; 100°) also gives I in high yields. Therefore, it appears that both the fluorene nucleus and the aliphatic carbon attached to the nitrogen of the aralkylamino intermediate (—NH—CH_2—Ar) are brominated. Dehydrobromination leads to the formation of I.

Oxidation of the aralkyl bromides to aldehydes in dimethyl sulfoxide[3] followed by condensation with the amine does not seem to take place, at least to any appreciable extent, because we find that aralkylation of the amine takes place more readily than oxidation of the aralkyl bromide. For example, 2-aminofluorenone and *p*-bromobenzyl bromide in dimethyl sulfoxide at room temperature for 5 or 8 days yields neither *p*-bromobenzaldehyde nor the azomethine. The main products are the *N*-monoaralkylated-3-bromo- and diaralkylated 2-aminofluorenones.

The reaction of 2-aminofluorenone and some substituted 9-bromofluorenes in dimethyl sulfoxide at 100° gives intermediates of type II in high yields. The bromine is aliphatic, is not detectable in alcoholic solution with starch-iodide or alcoholic silver nitrate, but is removed with hot alcoholic potassium hydroxide (*anal.*, for example with Y = $NHCOCF_3$, found for $C_{28}H_{16}BrF_3H_2O_2$: C, 60.88; H, 2.96; N, 4.82 Br, 14.82). *p*-Nitroaniline similarly gives *N*-9′-(9′-bromofluorenyl)-*p*-nitroaniline.



Bromination of 2-*N*-(9′-fluorenyl)aminofluorenones with 48% hydrobromic acid in dimethyl sulfoxide or with *N*-bromosuccinimide (UV) gives II. 2-*N*-(9′-Fluorenyl)amino-3-bromofluorenone and *N*-bromosuccinimide (UV) gives 2-amino-3-bromofluorenone hydrobromide, which indicates that bromination of the carbon α to the amine, followed by formation of an azomethine by oxidative dehydrobromination is, in turn, followed by cleavage to give the 2-amino-3-bromo compound.

We have found, therefore, a new type of oxidation (to azomethines) of certain secondary amines by way of a brominated intermediate. The secondary amine may be used as such or it may be formed as a first step in the reaction. With some types we can isolate this intermediate, brominated on the same carbon atom from which bromine was removed in the formation of the secondary amine.

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