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Racemization of Phenylalkanes in Presence of Lewis Acids

ERNEST L. ELIEL, PHILIP H. WILKEN,[1] AND FABIAN T. FANG

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Optically active 2-phenylbutane racemizes rapidly and completely in the presence of aluminum chloride at 0°C. at which temperature there is little disproportionation to *m*- and *p*-di-*sec*-butylbenzene. Racemization appears to be due to formation of the 2-phenyl-2-butylcarbonium ion followed by transfer of a hydride ion from a 2-phenylbutane molecule in a chain reaction, since in the presence of α,β-dideuterocumene, substantial amounts of deuterium are transferred to the 2-phenylbutane. Optically active α-deuteroethylbenzene is not completely racemized under much more drastic conditions.

Burwell and Shields[2] have recently reported on the racemization of 2-phenylpentane in the presence of aluminum chloride. In the course of an investigation which was nearly complete when we learned of the prior work of Burwell and Shields we have confirmed and extended certain observations of these authors using 2-phenylbutane and α-deuteroethylbenzene as substrates.

When active 2-phenylbutane was heated with aluminum chloride at 100°, it was extensively disproportionated to benzene and a dialkylbenzene fraction which proved to be a mixture of the *meta* and *para* isomers. The recovered starting material was completely racemized. *A priori*, two mechanisms might be suggested for the racemization; one (a) in which the alkyl group comes off as a carbonium ion and then returns and another (b) involving a hydride transfer chain from an alkylbenzene to an aralkyl carbonium ion:[3a]

$$d\text{-}C_6H_5CH(CH_3)C_2H_5 + AlCl_3 + HCl \longrightarrow C_6H_6 + dl\text{-}CH_3C^+HC_2H_5 + AlCl_4^- \longrightarrow dl\text{-}C_6H_5CH(CH_3)C_2H_5 + AlCl_3 + HCl \quad (a)$$

$$d\text{-}C_6H_5CH(CH_3)C_2H_5 + AlCl_3 + HCl \longrightarrow dl\text{-}C_6H_5C^+(CH_3)C_2H_5 + AlCl_4^- + H_2$$
$$dl\text{-}C_6H_5C^+(CH_3)C_2H_5 + d\text{-}C_6H_5CH(CH_3)C_2H_5 \longrightarrow dl\text{-}C_6H_5CH(CH_3)C_6H_5 + dl\text{-}C_6H_5C^+(CH_3)C_2H_5 \quad (b)$$

Burwell and Shields[2] have already pointed out (for the case of 2-phenylpentane) that mechanism (b) is more likely since racemization takes place under conditions where transalkylation (which may involve the 2-pentylcarbonium ion[3b]) is almost inoperative. In the case of 2-phenylbutane, complete racemization occurs with aluminum chloride in 12 hr. at room temperature and even in 2 hr. at ice-bath temperature, though in the latter case the yield of transalkylation product is reduced to 9%.

A more compelling argument for mechanism (b) was obtained from a treatment of equimolar amounts of 2-phenylbutane and α,β-dideuterocumene with aluminum chloride at ice-bath temperature. The recovered 2-phenylbutane contained 0.28 atom of deuterium per molecule as indicated by mass spectrometry. Statistical distribution of the α-deuterium and α-hydrogen atoms among the cumene and 2-phenylbutane molecules should have given 2-phenylbutane containing 0.50 atom of

(1) Peter C. Reilly Fellow, 1952–53; Socony Vacuum Fellow, 1953–54. This work is taken in part from the Ph.D. dissertation of P. H. W. and was presented before the Organic Division of the American Chemical Society at Minneapolis, Minnesota, on September 14, 1955.

(2) R. L. Burwell, Jr., and A. D. Shields, *J. Am. Chem. Soc.*, **77**, 2766 (1955).

(3) (a) The initiation step in mechanism (b) is not definitive; several reasonable alternatives exist. The inclusion of HCl in the initiation steps requires comment: no hydrochloric acid was added to the reaction mixture, but the formation of traces of this reagent due to adventitious moisture is quite likely. (b) This point is arguable in the case of a secondary alkyl group; *cf.* D. A. McCaulay and A. P. Lien, *J. Am. Chem. Soc.*, **75**, 2411 (1953); H. C. Brown and C. R. Smoot, *Ibid.*, **78**, 2176 (1956); H. C. Brown and H. Jungk, *Ibid.*, **78**, 2182 (1956). However, even if the transalkylation is an S_N2 reaction, a version of mechanism (a) can be written which will lead to racemization: $2d\text{-}C_6H_5R^* \rightarrow meso\text{-}C_6H_4R_2^* + C_6H_6 \rightleftharpoons 2dl\text{-}C_6H_5R^*$ where R* is an asymmetric alkyl group such as 2-butyl.

deuterium; the discrepancy is undoubtedly due to the fact, evident from mass spectrum and elementary deuterium analysis, that the α,β-dideuterocumene used in this investigation was not isotopically pure.

When optically active α-deuteroethylbenzene[4] was heated with aluminum chloride at 65–70° for several hours, the recovered starting material still retained one third of its original activity.[5] This fact is consistent with mechanism (b) [though it does not exclude (a)], since a hydride transfer reaction involving the secondary α-phenethyl carbonium ion:

$$dl\text{-}C_6H_5C^+DCH_3 + d\text{-}C_6H_5CHDCH_3 \longrightarrow dl\text{-}C_6H_5CHDCH_3 + dl\text{-}C_6H_5C^+DCH_3 \quad (c)$$

should involve higher activation energy than the corresponding reaction [Equation (b)] involving the tertiary 2-phenylbutyl carbonium ion.[6]

One of our experiments involving racemization of 2-phenylbutane was carried out under conditions identical with those used[7] in the alkylation of benzene with optically active butanol-2 in the presence of aluminum chloride. The fact that 2-phenylbutane racemizes totally under these conditions while it does not racemize extensively in the presence of boron trifluoride[8] may explain why Price and Lund obtained slightly active material in the alkylation of benzene with active butanol-2 in the presence of boron trifluoride but not with aluminum chloride which yielded totally racemized product.[7]

It is of interest that although 2-phenylbutane is racemized rapidly by aluminum chloride, we have found that it can be acetylated to give an optically active product with acetyl chloride in the presence of aluminum chloride. The same is true of 2-phenylpentane[9] and of α-deuteroethylbenzene.[4] Probably the acetyl chloride as well as the ketone formed in the acylation complexes with the catalyst in such a way as to make it ineffective for the promotion of reaction sequence (b).

A few improvements were made in the synthesis of active 2-phenylbutyric acid required as an intermediate for active 2-phenylbutane. The reaction sequence employed was the following:

$$PhCH_2CH_3 \longrightarrow PhCHBrCH_3 \longrightarrow PhCH(CH_3)CH(CO_2Et)_2 \longrightarrow PhCH(CH_3)CH(CO_2H)_2 \longrightarrow PhCH(CH_3)CH_2CO_2H$$

Ethylbenzene was brominated photochemically in 81% yield employing carbon tetrachloride as a solvent. Alkylation of malonic ester with the bromide was effected in 82% yield by using sodium hydride as the base and a mixture of benzene and dimethylformamide as solvent.[10] Decarboxylation of the malonic acid was effected conveniently in boiling 2,6-lutidine. In the resolution of β-phenylbutyric acid (best effected by means of α-phenethylamine) it was found convenient to let the racemate crystallize from a petroleum ether solution of the partly resolved material. This increased the optical purity of the acid from 56 to 76%.

EXPERIMENTAL[11]

α-Phenethylmalonic ester. A suspension of 26 g. (1.13 g. atom) of sodium hydride in 800 ml. of sodium-dried benzene and 300 ml. of pure dimethylformamide (technical material was azeotropically distilled with benzene, b.p. 150–150.5°) in a three-necked flask equipped with stirrer, reflux condenser and dropping funnels, was cooled to 5–10° under a slow stream of nitrogen. Ethyl malonate (180 ml., 190 g., 1.19 mole) diluted with its own volume of benzene, was added at such a rate that hydrogen was evolved gently. After the solution had become homogeneous, 201 g. (1.08 mole) of α-phenethyl bromide[12] was added and the temperature gradually raised to 75–80° and maintained there for 2 hr. by the application of a hot water bath. The mixture was then cooled, washed with water in a separatory funnel, and the water layer twice extracted with benzene. The combined benzene layers were washed twice with dilute hydrochloric acid, once with water, once with 10% aqueous sodium carbonate, and again with water, dried over sodium sulfate, concentrated, and the residue distilled at reduced pressure. The product boiling at 131–133°/0.8 mm. (lit.[13] 138°/1.5 mm.) weighed 234.1 g. (82%).

β-Phenylbutyric acid. The above ester (132 g., 0.5 mole) was boiled under reflux for 1 hr. with a solution of 118 g. (2 moles) of potassium hydroxide in one liter of 95% ethanol. The alcohol was then distilled on a steam bath and replaced by water, 250 ml. of water being added each time 250 ml. of distillate had been collected until the total distillate amounted to almost one liter. The aqueous solution was then poured into an excess (4–5 moles) of concentrated hydrochloric acid[14] and the α-phenethylmalonic acid which precipitated was collected and dried, m.p. 142–143° (lit.[13] 142–143°); yields as high as 92% were obtained.

(4) E. L. Eliel, *J. Am. Chem. Soc.*, **71**, 3970 (1949).

(5) The diethylbenzene fraction isolated from this experiment was inactive. We are continuing the study of the optical course of the Friedel-Crafts transalkylation as well as the rearrangement reaction.

(6) Only hydride transfer is shown in equation (c) for the sake of clarity. A lesser amount of deuteride transfer is, of course, an alternative possibility and would also lead to racemization. The formation of light ethylbenzene and ethylbenzene-α,α-d_2 in the disproportionation is to be expected.

(7) C. C. Price and M. Lund, *J. Am. Chem. Soc.*, **62**, 3105 (1940).

(8) R. L. Burwell, Jr., L. M. Elkin, and A. D. Shields, *J. Am. Chem. Soc.*, **74**, 4570 (1952).

(9) D. J. Cram, *J. Am. Chem. Soc.*, **74**, 2152 (1952). Complete absence of racemization in the acetylation step was demonstrated in this case.

(10) This excellent technique was first described by A. W. Burgstahler, Ph.D. dissertation, Harvard University, 1953.

(11) All melting and boiling points are uncorrected. Mass spectrometric analyses were carried out by Mr. George Young on a Consolidated 21-103A Analytical Mass Spectrometer, employing an ionization potential of 70 volts. Infrared spectra were recorded by Anthony Verbiscar and Rolland Ro on a Baird double-beam instrument.

(12) Prepared in 81% yield by brominating ethylbenzene (159 g.) in 300 ml. carbon tetrachloride by the addition of 240 g. bromine in 150 ml. carbon tetrachloride under illumination with a 1000-watt unfrosted tungsten projector lamp.

(13) E. Bergmann, *Helv. Chim. Acta*, **20**, 590 (1937).

(14) Addition of the acid to the aqueous solution may lead to precipitation of the monopotassium salt.

The malonic acid (170 g.) was boiled with 250 ml. of 2,6-lutidine[15] for 2 hr., the solution was cooled and poured into an excess of 20% hydrochloric acid, and the aqueous emulsion was extracted four times with ether. The combined ether layers were extracted four times with dilute hydrochloric acid, then with water, dried over sodium sulfate, and concentrated. 3-Phenylbutyric acid boiled at 118–119°/0.8 mm. (lit.[13] 140–141°/2 mm.); n_D^{25} 1.5140 and crystallized to a solid melting at 35–36° (lit.[16] 39–40°). The yield in several preparations varied from 87 to 91%. With thermal decarboxylation[13] the yield was only 71%.

Partial resolution of β-phenylbutyric acid. To a solution of 141.6 g. (0.86 mole) of β-phenylbutyric acid in 385 ml. of ethanol and 412 ml. of water was added 104.1 g. (0.86 mole) of (+)-α-phenethylamine.[17] An exothermic reaction ensued and within 5 min. needle-shaped crystals began to separate. Crystallization was allowed to proceed undisturbed and the amine salt (114.7 g.) was collected; m.p. 138–141°. No attempt was made to purify the salt, since optically pure materials were not needed in the present work. The mother liquor from this salt became cloudy during filtration and was heated to produce a clear solution which deposited crystals (40.0 g., m.p. 127–129.5°) on standing in the refrigerator. The crystals were removed and the resulting solution was evaporated almost to dryness and cooled, whereupon a third crop of crystals separated and was collected, weight 97.5 g., m.p. 119–121°.

The various crops of amine salts were separately dissolved in warm methanol and the solution was poured into an excess of dilute hydrochloric acid. The free β-phenylbutyric acid separated as an oil and was extracted with three portions of ether which were then combined and washed once with dilute hydrochloric acid and once with water, dried over sodium sulfate, and concentrated and distilled at reduced pressure. The following fractions of resolved acid were thus obtained:

From Fraction	Wt. (G.)	%	B.P./0.8 Mm.	n_D^{25}	α_D^{25} (l = 1 Dm., Neat)
I	50	35	115–117°	1.5140	−32.42°
II	17.3	12.2	115–117°	1.5135	+ 1.31°
III	46.2	33	115–117°	1.5140	+35.38°

Since the rotation of the pure acid is 56.5°,[20] fraction I was 57% optically pure and fraction III was 62.5% optically pure. The optical purity could be increased as follows: Ten g. of acid, α_D^{25} −32.42° was dissolved in 20 ml. of Skellysolve B. The solution was chilled to 0° and seeded with a crystal of the *dl* acid. After 24 hr., the bottom of the flask was covered with crystals. The solution was decanted and concentrated. The residue had α_D^{25} −43.06° (l = 1 dm., neat) corresponding to 76% optical purity.

Addition of base to the acidic aqueous layer obtained in the decomposition of the diasteroisomeric salt led to recovery of most of the α-phenethylamine used in the resolution.

Active 2-phenylbutane. The active β-phenylbutyric acid was reduced to 3-phenylbutanol in 80% yield by means of lithium aluminum hydride.[20] The alcohol had b.p. 132.5–135°/18–19 mm., n_D^{25} 1.5184; lit.[20] b.p. 138–140°/33 mm., n_D^{25} 1.5186. Conversion of this alcohol to the bromide by means of phosphorus tribromide[21] was effected in 80–84% yield and the product boiled at 134–135°/26 mm., n_D^{25} 1.5350; lit.[20] n_D^{25} 1.5350.

The reduction of 21.1 g. (0.1 mole) of the bromide by means of 0.5 g. (0.013 mole) of lithium aluminum hydride and 1.2 g. (0.15 mole) of lithium hydride in 50 ml. of tetrahydrofuran was effected in the usual way,[22] reflux time 4 hr. The reaction mixture was worked up in the usual way with the inclusion of a phosphoric acid wash to remove any residual tetrahydrofuran[4] and the product was obtained in 86–89% yield, b.p. 168–170°, n_D^{25} 1.4870 (lit.[23] n_D^{25} 1.4863–1.4880; b.p. 172.5°). The infrared spectrum of the material so obtained was identical with that reported in the literature.[24]

In this series of transformations, β-phenylbutyric acid of α_D^{25} +25.28° (l = 1 dm., neat) gave 2-phenylbutane of α_D^{25} +21.83° (l = 2 dm., neat). The ratio of the observed rotation of product (corrected to a 1-dm. tube) to that of starting material is 0.43, exactly the same as that reported in the literature[20] for very slightly different temperatures.

p-sec. Butylacetophenone. This was prepared in 90% yield by the Perrier modification of the Friedel-Crafts Reaction[25] and boiled at 142–143°/17 mm., n_D^{20} 1.5195, n_D^{25} 1.5178; lit.[26] b.p. 134–135°/11 mm., n_D^{20} 1.5195. The 2,4-dinitrophenylhydrazone melted at 145.5–147°; lit.[27] 146–147°. Optically active 2-phenylbutane of α_D^{25} +21.83° (l = 2 dm., neat) gave ketone having α_D^{25} −15.73° (l = 1 dm., neat).

Cumene-α,β-d₂. The catalytic reduction of α-methylstyrene with deuterium was carried out in a low-pressure apparatus made by the Parr Instrument Co. of Moline, Ill. The tank was flushed thoroughly with nitrogen before the admission of deuterium gas.

A solution of 23.6 g. (0.200 mole) of freshly distilled α-methylstyrene, b.p. 62.6–62.9° (19 mm.), in 150 ml. of absolute ethanol was first reduced in the presence of 0.40 g. of platinum oxide catalyst at 24.4° and an initial deuterium pressure of 26.9 lb. The calculated amount of deuterium was absorbed within 10 min.

A second portion of 35.5 g. (0.300 mole) of the same unsaturated compound in 150 ml. of ethanol was then reduced in the presence of 0.50 g. of catalyst at 25.0° and an initial deuterium pressure of 34.8 lb. The absorption took 17 min.

The reduction mixtures were filtered in the usual manner. The combined ethanolic filtrates were poured into 1.5 l. of water and the aqueous mixture was extracted twice with pentane. The pentane solution was washed with water and 20% calcium chloride solution, dried over anhydrous calcium chloride, and then fractionated through a 20-cm. glass helices-packed column to give 51.7 g. (84.6%) of cumene-α,β-d₂, b.p. 150.0–151.5° (747 mm.), n_D^{20} 1.4902. (Pure cumene has b.p. 152.4/760 mm. and n_D^{20} 1.4915.[23])

(15) We are indebted to Dr. Frank Cislak of the Reilly Tar and Chemical Corp. for a generous gift of 2,6-lutidine.

(16) H. Rupe, *Ann.*, **369**, 323 (1909).

(17) The amine was resolved by means of pyroglutamic acid[18] which, in turn, was prepared by pyrolysis of commercial glutamic acid.[19] Since this work was completed, a very convenient method for the resolution of α-phenethylamine with D-tartaric acid has been published: W. Theilacker and H. G. Winkler, *Ber.*, **87**, 690 (1954).

(18) R. J. Dearborn and J. A. Stekol, U. S. Patent **2,528,267** (1950); *C. A.*, **45**, 2984d (1951).

(19) G. Braun, U. S. Patent **2,112,329** (1938); *C. A.*, **32**, 3773 (1938).

(20) D. J. Cram, *J. Am. Chem. Soc.*, **74**, 2137 (1952).

(21) P. A. Levene and R. E. Marker, *J. Biol. Chem.*, **108**, 413 (1935).

(22) J. E. Johnson, R. H. Blizzard, and H. W. Carhart, *J. Am. Chem. Soc.*, **70**, 3664 (1948).

(23) G. Egloff, *Physical Constants of Hydrocarbons*, Vol. III, Reinhold, New York, N. Y., 1946.

(24) N.R.L. Report No. C-3274 of the Navy Research Laboratory, Washington, D. C., pp. 84–85.

(25) D. T. Mowry, M. Renoll, and W. F. Huber, *J. Am. Chem. Soc.*, **68**, 1105 (1946).

(26) G. F. Hennion and S. F. de C. McLeese, *J. Am. Chem. Soc.*, **64**, 2421 (1942).

(27) D. V. Nightingale, H. B. Hucker, and O. L. Wright, *J. Org. Chem.*, **18**, 244 (1953).

Anal. C_9H_{12}, 24.3, 24.1%; $C_9H_{11}D$, 39.4, 40.0%; $C_9H_{10}D_2$, 24.8, 25.1%; $C_9H_9D_3$, 6.9, 6.8%; $C_9H_8D_4$, 2.8, 2.7%; $C_9H_7D_5$, 1.2, 1.0%; $C_9H_6D_6$, 0.5, 0.2%; $C_9H_5D_7$, 0.0, 0.1%. This composition, determined by mass spectrometry at reduced ionizing voltage,[28] corresponds to a deuterium content of 10.8 (first analysis) or 10.7 (second analysis) atom %; found 10.6%.[29]

Treatment of active 2-phenylbutane with aluminum chloride. 2-Phenylbutane (40.5 g.), α_D^{25} +1.53° (l = 1 dm., neat) was placed in a 125-ml. three-necked flask equipped with a sealed stirrer and an outlet protected by a drying tube and cooled in an ice bath for 30 min. Eight g. of aluminum chloride was then added and the suspension stirred for 2 hr. at ice bath temperature. The mixture was then poured onto 100 g. of ice and 20 ml. of concentrated hydrochloric acid and the organic layer was separated, dried over calcium chloride and fractionated. There was recovered 28.8 g. (71%) of 2-phenylbutane, b.p. 55–57°/11 mm., n_D^{25} 1.4870. The material was collected in two fractions which had the same refractive index. The rotation of the first fraction was found to be 0.00°. Higher boiling material (b.p. 105–108°/11 mm., n_D^{25} 1.48±8) weighed 2.6 g. (9% calculated as *di-sec.* butylbenzene).

When the reaction was carried out at ice bath temperature as above, followed by standing at room temperature for 12 hr., inactive material was again obtained. Recovered starting material, b.p. 54–56°/11 mm., n_D^{25} 1.4870 weighed 19.0 g. (47%). There was also obtained 7.9 g. (28%) of material boiling at 102–108°/11 mm., n_D^{25} 1.4842. The infrared spectrum of the lower-boiling fraction was identical with that of the starting material.

In a reaction of 80 g. (0.6 mole) of 2-phenylbutane, α_D^{25} +2.16° (l = 1 dm., neat) with 16 g. of aluminum chloride at 100° for 3 hr. there was obtained 10.6 g. (23%) of benzene, b.p. 78–81°, n_D^{25} 1.4925 (lit. b.p. 80°, n_D^{25} 1.4981), 29.7 g. (37%) of recovered 2-phenylbutane, b.p. 53–60°/11 mm., n_D^{25} 1.4862–1.4866, α_D^{25} (of various fractions) 0.00–0.02° (l = 1 dm., neat) and 16.8 g. (30% calculated as di-*sec.* butylbenzene) of fractions boiling from 102–114°/11 mm., n_D^{25} 1.4840–1.4848, n_D^{25} 0.00–0.02°.

The low-boiling fraction was identified as benzene by the preparation of *m*-dinitrobenzene, m.p. 90–91° (lit. 90°). The intermediate fractions had infrared spectra almost identical to that of 2-phenylbutane but showing slight contamination which manifested itself especially in a strong band at 13.6 μ. The high-boiling fractions were probably mixtures of *m*- and *p-di-sec.*butylbenzene as evidenced by the infrared spectrum (band at 12.1 μ due to *p*-isomer, bands at 12.7 and 14.2 μ due to *m*-isomer[30]) and the fact that permanganate oxidation followed by esterification with diazomethane gave a mixture of esters from which dimethyl terephthalate, m.p. 138–141° (lit. 140°) undepressed by admixture of an authentic specimen, was isolated.

Treatment of an equimolar mixture of 2-phenylbutane and cumene-α,β-d_2 with aluminum chloride.[31] A mixture of 20.13 g. (0.15 mole) of *dl*-2-phenylbutane and 18.33 g. (0.15 mole) of cumene-α,β-d_2 was stirred with 5.00 g. of anhydrous aluminum chloride at ice-bath temperature for 2 hr. and then poured onto ice and hydrochloric acid. The aqueous acidic mixture was extracted three times with pentane. The combined pentane extracts were washed with water, dried over calcium chloride, freed of solvent, and then distilled through a 20-cm. glass helices-packed column. A fraction boiling at 170.0–172.6 (746 mm.) n_D^{20} 1.4894 was considered as recovered 2-phenylbutane and analyzed by mass spectrometry at reduced ionizing voltage.[28]

Anal: $C_{10}H_{14}$, 73.0, 73.3%; $C_{10}H_{13}D$, 25.2, 25.2%; $C_{10}H_{12}D_2$, 1.8, 1.5%.[32]

Disproportionation of (+)-ethylbenzene-α-d with aluminum chloride. A mixture of 7.7 g. (0.072 mole) of (+)-ethylbenzene-α-d,[4] α_D^{25} +0.49 ± 0.01°, and 1.8 g. of anhydrous aluminum chloride (Baker and Adamson, reagent grade) was stirred at room temperature for 15 min. and then heated up to and maintained at 65–70° while a reduced pressure of 100 mm. was applied to the system. The benzene thus distilled out and collected in a cold trap weighed 0.83 g. (0.0106 mole). The dark brown reaction mixture was allowed to cool at the end of 1 hr. and then poured onto crushed ice. The aqueous mixture was extracted with one 50-ml. and two 25-ml. portions of ether. The combined ethereal extract was washed with water, dried over sodium sulfate, freed of the solvent, and then fractionated to give 1.23 g. (0.0115 mole) of ethylbenzene-α-d, b.p. 59–60° (50 mm.), and 1.79 g. (0.0131 mole) of deuterated diethylbenzenes, b.p. 96–97° (50 mm.). The mixture of diethylbenzenes was optically inactive, α_D = 0.00 ± 0.02°, whereas a solution of one volume of the recovered ethylbenzene in two volumes of pentane had a rotation of α_D = +0.05 ± 0.01° (1-dm. tube). A similar solution of the original ethylbenzene-α-d in pentane had α_D = +0.16 ± 0.01°.

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(28) D. P. Stevenson and C. D. Wagner, *J. Am. Chem. Soc.*, 72, 5612 (1950).

(29) Hydrogen-deuterium exchange with the solvent as well as with the cumene and α-methylstyrene presumably accounts for the undeuterated, monodeuterated, and polydeuterated material; *cf.* E. L. McDaniel and H. A. Smith, *Advances in Catalysis*, Vol. IX, Academic Press, New York, N. Y., in press and R. L. Burwell, Jr., and A. B. Littlewood, *J. Am. Chem. Soc.*, 78, 4170 (1956).

(30) *cf.* G. F. Hennion, A. J. Driesch, and P. L. Dee, *J. Org. Chem.*, 17, 1102 (1952).

(31) We thank Professor C. C. Price for suggesting this experiment.

(32) The value for the di-deuterated material, though small, appears to be real and suggests a small amount of exchange at a position other than the *alpha*-position in the side-chain—probably in the aromatic ring.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NOTRE DAME AND THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PENNSYLVANIA]

Some Derivatives of Malondialdehyde

T. L. V. ULBRICHT[1] AND CHARLES C. PRICE[2]

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Sodium nitromalondialdehyde (NMA), prepared by several methods, has been condensed with *p*-aminobenzoic acid (PABA) and its methyl ester. The further condensation of these products, and of NMA, with certain pyrimidines in order to give pteridines, has been investigated. Some similar reactions with malondialdehyde tetramethyl acetal (MTA) have also been studied. Infrared data from some of the compounds are reported.

Pteroylglutamic acid has been synthesized in a number of laboratories.[3] Many of these syntheses are based on the simultaneous condensation of the triaminopyrimidine (I), a three-carbon intermediate (II) with a reactive group (X, Y, Z, *e.g.*, halogen, ketone, hydroxyl) at each carbon atom (as in e.g., dibromopropionaldehyde, reductone, etc.), and *p*-aminobenzoylglutamic acid (III). As each reactive group may theoretically condense with any of the amino groups, many different reactions, leading to the formation of various isomers, are possible; this usually leads to considerable difficulties in the purification of the product. It is only recently that a synthesis has been reported[3l] in which intermediates of high purity were isolated.

It seemed worthwhile to investigate the condensation of a 4-amino-5-nitrosopyrimidine (IV), with a suitable three-carbon intermediate (V) and III, to see if by this means the formation of isomers could be avoided. That this type of reaction is feasible has subsequently been shown by Timmis and his coworkers[4]; however, all their products were 6,7-disubstituted pteridines, most of them polynuclear compounds.

It was decided to investigate malondialdehyde derivatives as intermediates in the proposed reaction. Nitromalondialdehyde (NMA) may be prepared in somewhat variable yield (about 35%)[5] from mucobromic acid, which is tedious to prepare.[6] We have found that it may be prepared from two commercially available compounds, β-bromo-α-chloro-β-formylacrylic acid (in 26% yield) and from mucochloric acid (in 13% yield). NMA condenses with PABA to give *p-(2-formyl-2-nitroethylideneamino)benzoic acid* (VI) and a small quantity of the di-condensation product, *p*-[3-(*p'-carboxyphenyl-*)*imino-2-nitropropylideneamino*]*benzoic acid* (VII). Similarly, with PABA methyl ester, NMA

(1) Eli Lilly Postdoctoral Fellow, University of Notre Dame, 1953–54; Postdoctoral Fellow, University of Pennsylvania, 1954–55; present address: Dept. of Pharmacology, Yale University School of Medicine, 333 Cedar Street, New Haven, Conn.

(2) Present address: John Harrison Laboratory of Chemistry, University of Pennsylvania, Philadelphia 4, Pa. Supported in part by U.S.P.H.S. Grant CY-2189.

(3) (a) Waller, Hutchings, Mowat, Stockstad, Boothe, Angier, Semb, SubbaRow, Cosulich, Fahrenbach, Hultquist, Kuh, Northey, Seeger, Sickles, and Smith, *J. Am. Chem. Soc.*, **70**, 19 (1948); (b) Hultquist, Kuh, Cosulich, Fahrenbach, Northey, Seeger, Sickles, Smith, Angier, Boothe, Hutchings, Mowat, Semb, Stockstad, SubbaRow, and Waller, *J. Am. Chem. Soc.*, **70**, 23 (1948); (c) Angier, Stockstad, Mowat, Hutchings, Boothe, Waller, Semb, SubbaRow, Cosulich, Fahrenbach, Hultquist, Kuh, Northey, Seeger, Sickles, and Smith, *J. Am. Chem. Soc.*, **70**, 25 (1948); (d) Boothe, Waller, Stockstad, Hutchings, Mowat, Angier, Semb, SubbaRow, Couslich, Fahrenbach, Hultquist, Kuh, Northey, Seeger, Sickles, and Smith, *J. Am. Chem. Soc.*, **70**, 27 (1948); (e) Karrer and Schwyzer, *Helv. Chim. Acta*, **31**, 777 (1948); (f) Weygand, Wacher, and Schmied-Kowarzik, *Chem. Ber.*, **82**, 25 (1949); (g) Weygand and Schmied-Kowarzik, *Chem. Ber.*, **82**, 333 (1949); (h) King and Spensley, *J. Chem. Soc.*, 144 (1952); (i) Forrest and Walker, *J. Chem. Soc.*, 2002 (1949); (j) Tschesche, Korte, and Peterson, *Chem. Ber.*, **84**, 579 (1951); (k) Weisblat, Magerlein, Hanze, Myers, and Rolfson, *J. Am. Chem. Soc.*, **75**, 3625 (1953); (l) Sletzinger, Reinhold, Grier, Beachem, and Tishler, *J. Am. Chem. Soc.*, **77**, 6365 (1955).

(4) (a) Felton and Timmis, *J. Chem. Soc.*, 2881 (1954); (b) Spickett and Timmis, *J. Chem. Soc.*, 2887 (1954); (c) Osdene and Timmis, *J. Chem. Soc.*, 2214 (1955).

(5) P. E. Fanta, *Org. Syntheses*, **32**, 95 (1952).

(6) C. F. H. Allen and F. W. Spangler, *Org. Syntheses*, **27**, 60 (1947).

gives *methyl* p-(2-*formyl*-2-*nitroethylideneamino*)*benzoate* (VIII).

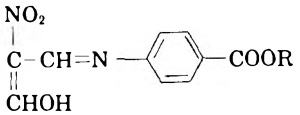
The condensation of NMA, VI, and VIII with a number of pyrimidines (see Table I) was investigated.

TABLE I
PYRIMIDINE SUBSTITUENTS

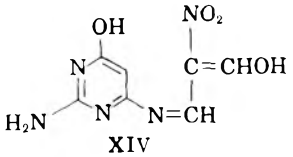
Compound	2	4	5	6	Reference
IV	NH_2	NH_2	NO	OH	7
X	CH_3S	NH_2	NO	OH	7
XI	NH_2	NH_2	NO	OC_2H_5	7
XII	NH_2	NH_2		OH	7
XIII	NH_2	NH_2	Br	OH	7

No condensation products could be isolated in a pure state from the reactions of NMA, VI, or VIII with the pyrimidines IV, X, or XI. The reactions with IV had to be carried out in aqueous alkali; with X and XI, which were used because of their greater solubility, acetic acid or sodium in ethylene glycol were used as media.

NMA condenses with (XII) to give 2-*amino*-6-*hydroxy*-4-(2′-*nitro*-2′-*formylethylideneaminopyrimidine* (XIV), isolated as the sodium salt. Acidification gave a colorless, highly insoluble solid. An attempted nitrosation led to the isolation of the free form of XIV. The condensation of VI with XII unexpectedly also gave XIV as the product. No reaction took place with XIII under the same conditions, the sodium salt of XIII being recovered.



VI R = H
VIII R = CH_3

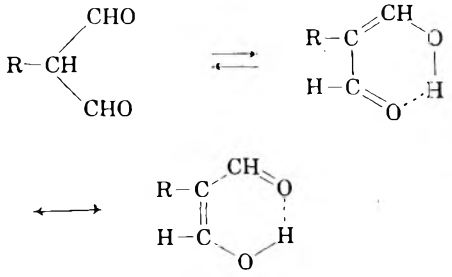


XIV

The reactivity and structure of malondialdehyde derivatives has received some attention. Most of these compounds do not very readily form dicondensation products, such as dianils or pyrimidines. Thus phenylmalondialdehyde (XV), and the closely related phenylmalononitrile and α-formylphenylacetonitrile, do not condense with guanidine.[8] XV gives only a monoanil[9] whereas the methyl ether of XV readily gives a dianil and reacts with guanidine to form a pyrimidine.[10] On the basis of these results, it has been suggested[9] that XV should be considered as hydroxymethylene phenylacetaldehyde.

(7) Ulbricht and Price, *J. Org. Chem.*, **21**, 567 (1956).
(8) Russell and Hitchings, *J. Am. Chem. Soc.*, **74**, 3443 (1952).
(9) Rupe and Knup, *Helv. Chim. Acta*, **10**, 299 (1927).
(10) Rupe and Knup, *Helv. Chim. Acta*, **30**, 846 (1927).

In a review,[11] Eistert mentions that bromomalondialdehyde (XVI) and reductone[12] (XVII) also give only monoanils, and these compounds all give enol ethers with diazomethane. He considers that the *cis*-enol form is stabilized by a chelate ring (see Figure 1) which can still be formed in the monoanil, but not in the dianil. (It is interesting to note that chloromalondialdehyde condenses with N-methylaniline to give a colorless product; all the other anils mentioned are yellow. No tautomerism, chelation, or conjugation with the benzene ring is possible in this compound.)



XV R = C_6H_5
XVI R = Br
XVII R = OH
XVIII R = NO_2

Fig. 1

NMA (XVIII), which, like the above malondialdehyde derivatives has an electron-withdrawing group on the central carbon atom, may be slightly more reactive; it gives a dianil with aniline, though only a monoanil with aniline hydrochloride.[13] Urea gives principally a mono-ureide, but guanidine, in the presence of piperidine, reacts to give a pyrimidine.[14] As has been shown, it gives mono- and di-condensation products with PABA. Nevertheless, it is clear that the first condensation takes place much more readily than the second, and that the second may not take place if the other reactant does not contain a sufficiently basic amino group. Consequently an attempt was made to methylate

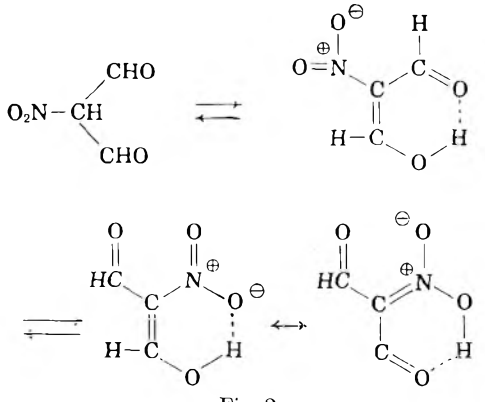


Fig. 2

(11) Eistert, *Arkiv. Kemi.*, **2**, 129 (1950).
(12) Reductone also gives a monocondensation product with PABA (Euler and Hasselquist, *Rec. trav. chim.*, **69**, 402 (1950)).
(13) Hill and Torrey, *Am. Chem. J.*, **22**, 89 (1899).
(14) Hale and Brill, *J. Am. Chem. Soc.*, **34**, 82 (1912).

XVIII with diazomethane, since the enol ether should be more reactive; but no product could be isolated. This may be because in NMA (and in a monocondensation derivative) tautomerism and chelation is also possible with the nitro group (see Figure 2) to give a nitronic acid.

Malondialdehyde tetramethyl acetal (MTA) condenses with PABA to give *p-(2-formylethylideneamino)benzoic acid* (XIX); difficulties in purification were probably due to the simultaneous formation of the di-condensation product, though this was not isolated (some higher-melting material, however, was obtained). With tosyl-PABA,[3k] which should only give a mono-condensation product, no reaction occurred. With the pyrimidine X in 90% formic acid, MTA reacted to give a product insoluble even in concentrated aqueous alkali.

Reaction appeared to occur between XIX and the pyrimidine XI, using sodium acetate in ethylene glycol, but no crystalline derivative could be isolated. The work of Spickett and Timmis[4b] indicated that the solubility of the nitrosopyrimidine was an important factor, *e.g.*, IV cannot be condensed with β-naphthol, though certain more soluble pyrimidines do react. The condensation of the more soluble XI with β-naphthol, using the conditions of Spickett and Timmis, was therefore carried out, but no pteridine was isolated.

Infrared data for some of the compounds are summarized in Table II.

TABLE II

INFRARED SPECTRA FOR VARIOUS COMPOUNDS IN POTASSIUM BROMIDE DISCS[a]

VI[b]		VIII[c]		XIV[d]		IV[e]		XII[f]	
ν	% Abs.	ν	% Abs.	ν	% Abs.	ν	% Abs.	ν	% Abs.
3100–2900	40	3200	39	3550	48	3300–3000	93	3260	87
1690	58	2940	24	3470	58			3230	83
1650	69	1725	72	3360	74	1700	93	3100–3060	94
1620	57	1680	26	3160	57	1610–30	95		
1600	77	1655	78	3050	55	1500	94	1550–1670	95
1570	74	1625	67	1570–1620	95	1355	81	1460	84
1480	56	1600	76	1500–25	93	1310	92	1365	81
1430	43	1580	74	1440–60	92	1255	91	1280	78
1355	65	1495	61	1485	51	1140–50	89	1245	65
1270–80	80	1430	53	1310–40	95			1175	45
1180	51	1310	86	1245	86			1135	50
1130	42	1265	90	1155	61				
		1175	58	1105	59				
		1120	40						
		1100	59						

[a] In a Perkin-Elmer twin beam instrument. [b] *p*-(2-Formyl-2-nitroethylideneamino)benzoic acid. [c] Methyl *p*-(2-formyl-2-nitroethylideneamino)benzoate. [d] 2-Amino-6-hydroxy-4-(2′-nitro-2′-formylethylideneamino)pyrimidine. [e] 2,6-Diamino-4-hydroxy-5-nitrosopyrimidine. [f] 2,6-Diamino-4-hydroxypyrimidine.

EXPERIMENTAL[15]

Mucobromic acid.[6] An improved yield is obtained by using furoic acid recrystallized from carbon tetrachloride (charcoal), and by concentrating the mother liquors from the reaction (in a hood). Yield, after recrystallization from water, 72% (lit.,[6] 60%).

Sodium nitromalondialdehyde (NMA) (XVIII). (a) *From mucobromic acid*[5]*:* Yield, about 35%.

(b) *From β-bromo-α-chloro-β-formylacrylic acid:* The acid (42.4 g.) in ethanol (100 ml.) was added to a solution of sodium nitrite (55.2 g.) in water (100 ml.) with stirring, at 58–60° during 30 min. Stirring was continued for 1 hr., without external heating. The solution was reheated to 60°, and left in the refrigerator overnight. The solid (11.2 g.) was filtered and crystallized from 75% ethanol, giving 7.14 g. (26%) of XVIII. In an experiment identical except that during the additional 1 hr. stirring the temperature was maintained at 60°, the yield was reduced to 18%.

(c) *From mucochloric acid:* Mucochloric acid (33.8 g.) was added in solution, as above, in 25 min., a little external cooling being necessary to keep the temperature from rising above 60°. After stirring for a further 35 min. and cooling overnight, the solid was filtered and extracted with boiling 75% ethanol (70 ml.), which, on cooling, gave 2.83 g. of NMA. The mother liquor was used to extract the residue, giving another 0.69 g.; total yield 3.52 g. (13%). No NMA at all was obtained when the reaction was carried out using twice the concentrations above, at 50–54°; nor when the addition was carried out at 35–40°, followed by raising the temperature to 58°.

p-(2-Formyl-2-nitroethylideneamino)benzoic acid (VI) *and p-(3-(p′-carboxyphenylimino)-2-nitropropylideneamino)benzoic acid* (VII). To a stirred solution of NMA (6.3 g.) in water (45 ml.) was added a solution of PABA (6.0 g.) in water (60 ml.) containing sodium hydroxide (1.9 g.) in 75 min. After standing for 5 hr., the solution was acidified with hydrochloric acid, filtered, and washed with water, and recrystallized from glacial acetic acid, giving yellow crystals of *p-(formyl-2-nitroethylideneamino)benzoic acid;* yield, 8.7 g. (82%). After further recrystallization from acetic acid it had m.p. 265°, dec.

Anal. Calcd. for $C_{10}H_8O_5N_2$: C, 50.9; H, 3.4; N, 11.8. Found: C, 51.3; H, 3.6; N, 12.0.

If the recrystallization is carried out so that not quite all the solid goes into solution, the residue may be recrystallized separately from acetic acid, giving a small variable quantity (about 300 mg.) of orange crystals of *p-(3-(p′-carboxyphenylimino)-2-nitropropylideneamino)-benzoic acid,* m.p. 329°, dec. (rapid heating after insertion at 315°).

(15) Melting points are uncorrected. Where no melting point is given, the compound either decomposes on heating, or does not melt below 300°. Analyses are by Microtech Inc., Skokie, Ill., and by Drs. Weiler and Strauss, Oxford, England.

Anal. Calcd. for $C_{17}H_{13}O_6N_3$: C, 57.4; H, 3.7; N, 11.8. Found: C, 57.0; H, 3.7; N, 12.1.

VII may also be prepared by the condensation of VI with PABA in methanol or aqueous alkali.

Methyl p-(2-formyl-2-nitroethylideneamino)benzoate (VIII). A solution of PABA methyl ester (5.1 g.) in aqueous methanol (80%, 50 ml.) containing piperidine (4 drops) was slowly added to a solution of NMA (4.7 g.) in aqueous methanol (60%, 75 ml.) with stirring, during 1.5 hr. After standing for 4 hr., the solution was concentrated under reduced pressure, during which the sodium salt of VIII crystallized. The mixture was acidified with 20 ml. of 2 *N* hydrochloric acid, filtered, and the product recrystallized from methanol. The yield of yellow crystals of *methyl p-(2-formyl-2-nitro-ethylideneamino)benzoate* was 6.26 g. (74%). It was purified by further crystallization from methanol, m.p. 186–188°.

Anal. Calcd. for $C_{11}H_{10}O_5N_2$: C, 52.8; H, 4.0; N, 11.2. Found: C, 52.7; H, 3.9; N, 11.3.

2-Amino-6-hydroxy-4-(2'-nitro-2'-formylethylideneamino)-pyrimidine (XIV). (a) *From NMA.* NMA (1.0 g.) and XII (1.0 g.) were heated together in water (10 ml.) for 1 hr. at 120° (oil bath). After cooling, the yellow sodium salt was filtered, giving 1.4 g. of the *sodium salt* of *2-amino-6-hydroxy-4-(2'-nitro-2'-formylethylideneamino)-pyrimidine.* The product was recrystallized from aqueous sodium hydroxide.

Anal. Calcd. for $C_7H_6O_4N_5Na.{}^1/_2H_2O$: C, 32.8; H, 2.7; N, 27.4; Na, 8.9. Found: C, 32.5; H, 2.6; N, 27.3; Na, 9.1.

(b) *From VI.* VI (1.0 g.) and XII (0.58 g.) in water (25 ml.) containing sodium hydroxide (0.39 g.) were refluxed for 15 min., and again after standing overnight. After cooling, 1 g. of yellow solid was collected. Recrystallization from dilute aqueous sodium hydroxide gave the pure *sodium salt* of *XIV.*

Anal. Calcd. for $C_7H_6O_4N_5Na\cdot{}^1/_2H_2O$: C, 32.8; H, 2.7; N, 27.4. Found: C, 32.6; H, 2.8; N, 27.3.

Attempted nitrosation of XIV; isolation of free XIV. To a solution of the sodium salt of XIV sodium nitrite was added, and the solution was acidified with acetic acid. A solid separated from the yellow solution, but there appeared to be no nitrosation (no change in color). The solution was heated until gas was evolved, and hydrochloric acid was then added until most of the solid dissolved. After filtration and cooling, ammonia was added to *p*H 7. The solid which separated was filtered and dried, and was *2-amino-6-hydroxy-4-(2'-nitro-2'-formylethylideneamino)pyrimidine.*

Anal. Calcd. for $C_7H_7O_4N_5$: C, 37.4; H, 2.9; N, 30.4. Found: C, 37.3; H, 3.1; N, 30.6.

p-(2-Formylethylideneamino)benzoic acid (XIX). To a solution of ammonium chloride (10 g.) in water (50 ml.) MTA (6.3 g.) was added. After stirring at 60° for 15 min., a solution of PABA (5.0 g.) in aqueous methanol (50%, 100 ml.) was added in 5 min. to the yellow solution, the color changing to reddish brown. Heating and stirring at 60° were continued for 25 min., and stirring at room temperature for 5 hr. The product was filtered, giving 6.2 g. of *p-(2-formylethylideneamino)-benzoic acid.* After several recrystallizations it was obtained as orange-brown crystals, m.p. 247–248°, dec.

Anal. Calcd. for $C_{10}H_9O_3N$: C, 62.8; H, 4.7; N, 7.3. Found: C, 62.3; H, 5.0; N, 7.8.

When the condensation was carried out in 50% methanol at 50°, most of the PABA was recovered unchanged. When 10% hydrochloric acid was used in place of ammonium chloride, at 60°, the yield was 7.3 g., but the product was darker and much more difficult to purify.

PHILADELPHIA, PA.

[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY, DE PAUL AND PURDUE UNIVERSITIES]

Improved Method for the Synthesis of Alkyl Azides[1]

EUGENE LIEBER,[2] TAI SIANG CHAO, AND C. N. RAMACHANDRA RAO

Received September 10, 1956

An improved method has been devised for the preparation of alkyl azides involving the use of Carbitols as solvents for the interaction of an alkyl halide and sodium azide. The method eliminates the hazards and restrictions of sealed tubes and the formation of troublesome azeotropes. Utility of the procedure is demonstrated by the preparation of seven *n*-alkyl- and two cycloalkyl azides with yields from 64.4 to 99.6%, considerably higher than previously reported. Five new *n*-alkyl azides are described: propyl, pentyl, heptyl, octyl, and decyl azides.

Although 1-azido-2-methylbutane (one of the amyl azides) has been prepared by Levene and Rothen[3] using a sealed tube reaction, pure pentyl azide has not been hitherto prepared. Inasmuch as it was desired as an intermediate, a study of its preparation was carried out. The name 1-azido-pentane can be found in *Chemical Abstracts.*[4] An examination of the original literature[5] disclosed that the product was really a mixture of isomeric amyl azides since it was prepared from mixed amyl iodides (b.p. 140–148°) and silver azide. The boiling point given[5] for the isomeric amyl azides was 121–130°.

Pentyl azide was prepared from pentyl iodide and activated sodium azide.[6] Precaution was taken to wash the pentyl iodide with saturated sodium sulfite solution and to distil it under vacuum in the presence of deposited silver. In order to avoid the use of a sealed tube, the reaction was carried out in boiling propyl alcohol. In working up the product mixture, an effort was made to remove the propyl alcohol by diluting with water and then extracting the ether solution with saturated salt solutions. However, due to the incomplete removal of propyl alcohol, considerable difficulty was encountered in isolating the desired pentyl azide. Although the

(1) This study was supported by a grant from the Office of Naval Research.

(2) De Paul University, to whom all requests for reprints and additional information should be addressed.

(3) Levene and Rothen, *J. Biol. Chem.*, 115, 415 (1936).

(4) *Chem. Abstrs.*, 46, 10440 (1952).

(5) Werle and Fries, *Biochem. Z.*, 322, 511 (1952).

(6) Smith, *Org. Reactions*, III, 382 (1946).

TABLE I
NORMAL ALKYL AZIDES

Alkyl	Yield, %	B.P., °C./Mm.	n_D^{20}	Anal. Calcd. % C	Anal. Calcd. % H	Anal. Calcd. % N	Anal. Found % C	Anal. Found % H	Anal. Found % N
C_3H_7	64.4	58/357	1.4105	42.33	8.29	49.38	42.51	8.09	49.53
C_4H_9	78.3	71/225	1.4192	48.46	9.15	42.39	48.31	9.12	42.39
C_5H_{11}[a]	83.6	63.5/95	1.4266						
C_6H_{13}	86.6	85/63	1.4318						
C_7H_{15}	99.6	70/13	1.4343	59.53	10.71	29.76	59.49	10.47	29.53
C_8H_{17}	94.8	62/3.3	1.4368	61.89	11.04		61.64	10.87	
$C_{10}H_{21}$	89.2	67/0.65	1.4425	65.52	11.55	22.93	65.33	11.40	23.13
Cyclopentyl	82.0	72/77	1.4616	54.03	8.16	37.81	53.98	8.27	37.85
Cyclohexyl	75.2	72/30	1.4693	57.57	8.86		57.51	8.88	

[a] Anal. for pentyl azide using propyl alcohol as solvent: Calcd. for $C_5H_{11}N_3$: C, 53.06; H, 9.80; N, 37.20. Found: C, 53.04; H, 9.92; N, 37.20.

boiling point of pentyl azide is 76.5°/110 mm., or approximately 130–135° at atmospheric pressure, it forms a low boiling azeotrope with propyl alcohol at 51–52°/103 mm. A number of redistillations were required until this was located and the azeotrope broken by means of toluene. The yield was 52%, comparable to that obtained by Henkel and Weygand[7] for hexyl azide. Boyer and Hamer[8] reported the formation of an azeotrope of butyl azide and methanol and also pointed out that the combination of butyl bromide and sodium azide without the use of solvent did not lead to the formation of butyl azide.

Owing to the difficulties described above, the problem of choosing a different solvent for this reaction was studied. The simple aliphatic alcohols were eliminated because of their tendency to form azeotropes with both the alkyl halide and the alkyl azide. Furthermore, the aliphatic alcohols require the use of sealed tubes, while the higher members are insoluble in water and do not dissolve sodium azide. Glycols are good in dissolving sodium azide and many members are miscible in water. However, their solubility for alkyl bromides and iodides is quite low. Our final selection, based upon these solubility considerations, was the alkyl ethers of polyethylene glycols. They were found to be ideally suited for the purpose. They dissolve all of the reactants and products and are easily removed by dissolving in water. A choice of suitable boiling points, considerably higher than those of the reactants and products, is available.

A preparation of pentyl azide was thus carried out in Carbitol, as solvent, by heating at 100° for 20 hr. The reaction mixture was then poured into water, whereupon the pentyl azide separated as an upper layer. No difficulty of azeotrope formation was encountered during the distillation, and an improved yield of 81.4% was obtained. The method is much more convenient than the sealed tube processes reported[7,9] for the preparation of these hazardous alkyl azides. Further studies indicated that the use of activated sodium azide was not necessary, commercial sodium azide giving the same yield of pentyl azide as that of freshly activated sodium azide.

The versatility of this improved procedure was then tested with a series of alkyl and cycloalkyl halides. The data obtained are summarized in Table I. Of these, the butyl,[8] hexyl,[7] cyclopentyl,[10] and cyclohexyl[10] azides have been previously reported. The high yield reported in Table I for heptyl azide was readily duplicated.

No decrease in yield was observed when an alkyl bromide was used in place of an alkyl iodide. The yield of butyl azide from butyl bromide was 78.3% and that from butyl iodide was 78.1%. Similarly, the yield of cyclopentyl azide from cyclopentyl bromide was 82%, while the yield of cyclohexyl azide from cyclohexyl iodide was 75.2%. Boyer, Canter, Hamer, and Putney,[10] using the procedure of Henkel and Weygand,[7] obtained yields of cyclopentyl and cyclohexyl azides of 51 and 68%, respectively.

Three different monoalkyl ethers of diethylene glycol were used. No appreciable difference was found between methyl Carbitol and Carbitol. They are both completely miscible with water and much less soluble in diethyl ether. Their solubility of sodium azide, sodium iodide, and alkyl azide was about the same. The boiling point of butyl Carbitol is 231°. It is less soluble in water and much more soluble in ether than its methyl or ethyl homolog. Slightly more water had to be used with butyl Carbitol in order to dissolve completely the sodium azide. The choice among these three solvents was based solely on the ease of separation. Thus, methyl Carbitol or Carbitol was used for alkyl azides boiling below 156° (hexyl azide), Carbitol for heptyl azide, and butyl Carbitol for octyl azide. For decyl azide, whose estimated[11] atmospheric boiling point is 230°, methyl Carbitol was used, and the small

(7) Henkel and Weygand, *Ber.*, **76**, 812 (1943).
(8) Boyer and Hamer, *J. Am. Chem. Soc.*, **77**, 951 (1955).
(9) Levene and Rothen, *J. Biol. Chem.*, **115**, 415 (1936); **120**, 759 (1937); **140**, 259 (1941).
(10) Boyer, Canter, Hamer, and Putney, *J. Am. Chem. Soc.* **78**, 325 (1956).
(11) *Vapor Pressure-Temperature Nomograph*, Nomo-Charts Company, P. O. Box 111, Roselle, New Jersey.

amount of it contained in the crude decyl azide was removed by distillation from the higher boiling azide.

Schard[12] has reported the preparation of isopropyl azide by the catalytic addition of hydrazoic acid to propylene. A number of C_4 to C_{10} secondary alkyl azides have been prepared by Levene and coworkers.[9] The latter invariably used sealed tubes to carry out the reaction between alkyl iodide and sodium azide. The yields obtained varied from 26.7% (for 2-ethylpentyl azide) to 81% (for 1-methylheptyl azide). When the sealed tube was not used, the yield of 2-methylhexyl azide was only 16.1% even after 60 hr. heating on a steam bath. The use of sealed tubes for alkyl azides is both hazardous and tedious. A violet explosion has been reported[13] on attempting to seal a tube containing methyl azide. The tediousness is due to the limited capacity of sealed tubes. The largest amount of azide reported[9] to be prepared was 17 grams of 2-ethylheptyl azide, for which seven sealed tubes had to be used. In another case,[9] nine tubes were used for the preparation of 13 grams of 2-ethylpentyl azide. The present method offers no such limitations and hazards. The capacity is limited only by safety considerations. The hazards of working with alkyl azides were considerably reduced by using water and by distillations under reduced pressure behind a safety barricade. No explosion or even noticeable decomposition of the azides was experienced.

EXPERIMENTAL[14]

Pentyl azide. Propyl alcohol as solvent. The pentyl iodide was purified by washing with three 50-ml. portions of a saturated Na_2SO_3 solution and two 50-ml. portions of water. The washed iodide was dried first with magnesium sulfate followed by Drierite. It was then vacuum distilled in the presence of metallic silver through a 13-in. column packed with glass helices. The fraction boiling 88–92°/100 mm., water white, n_D^{20} 1.4961 to 1.4970 was used. The sodium azide was activated by the method of Smith[11] and used at once after drying under vacuum at water-bath temperature.

A mixture comprising 32.2 g. (0.5 mole) of activated sodium azide, 400 ml. of propyl alcohol, and 80 ml. water was introduced into a 1-l., three-necked flask equipped with a stirrer, thermometer, and reflux condenser. The mixture was rapidly stirred and 99 g. (0.50 mole) of pentyl iodide was added dropwise over a period of 20 min. The mixture was heated to reflux (86–90°) for 24 hr. Considerable solid was present during the entire heating period. After cooling, the reaction mixture was diluted with 200 ml. of ether and poured slowly into 1 l. of water. The lower aqueous layer was extracted with two 200-ml. portions of ether, and the ether extracts were combined with the original upper layer and shaken with four 100-ml. portions of saturated $CaCl_2$ solution and three 100-ml. portions of saturated NaCl solution. The final ether solution was dried, the ether removed, and the residue fractionated under vacuum through the 13-in. packed column. A fraction having a constant boiling point of 51°/92 mm., and weighing 26.6 g., n_D^{20} 1.3862 showed by nitrogen analysis an azide content of only 3.8%. Four successive vacuum fractional distillations were required in order to locate and break the pentyl azide–propyl alcohol azeotrope. This turned out to be the fraction boiling 51–52°/103 mm., obtained in the initial distillation, the azeotrope being broken by addition of toluene and refractionation. The final yield of pentyl azide, b.p. 76.5/110 mm., n_D^{20} 1.4263 was 29.4 g. (52%).

Pentyl azide. Carbitol as solvent. A mixture comprising 27 g. of activated sodium azide, 450 ml. Carbitol, and 75 ml. of water was stirred in the apparatus previously used. Sixty g. (0.30 mole) of purified pentyl iodide was added in one batch. After stirring a few minutes, all of the reactants were completely dissolved. With constant stirring, the solution was heated up to 95° in 3 hr. and maintained at this temperature for an additional 20 hr. After cooling to room temperature, the reaction mixture was added to two 800-ml. portions of ice water. The lower aqueous layer was extracted with two 200-ml. portions of ether. The ether extracts were combined with the original upper layer, and the ether was removed. The residue of 42 g. was vacuum fractionated. Yield, 27.8 g. (81.4%), b.p. 77–78°/112 mm., n_D^{20} 1.4266. These values agree with the boiling point and the n_D^{20} of the pentyl azide described above. Repetition of this experiment with commercial sodium azide (E.K., P2352) (0.26 mole), purified pentyl iodide, 0.20 mole, 300 ml. of Carbitol, and 50 ml. of water, gave 18.9 g. (83.6%) of pentyl azide having the same boiling point and n_D^{20}.

Propyl azide, butyl azide, hexyl azide, heptyl azide, octyl azide, decyl azide, cyclopentyl azide, and *cyclohexyl azide.* These were prepared as described above. The experimental conditions are summarized below:

Azide	Moles NaN_3[a]	Moles Halide	Solvent Type	Ml.	Ml. H_2O
Propyl	0.4	0.3[b]	Methyl Carbitol	450	75
Butyl	0.4	0.3[c]	Methyl Carbitol	450	75
Hexyl	0.4	0.3[b]	Carbitol	450	75
Heptyl	0.26	0.2[b]	Carbitol	300	50
Octyl	0.26	0.2[b]	Butyl Carbitol	300	60
Decyl	0.26	0.2[b]	Methyl Carbitol	300	60
Cyclopentyl	0.26	0.2[c]	Carbitol	300	50
Cyclohexyl	0.40	0.3[b]	Carbitol	150	50

[a] Not activated. [b] Iodide. [c] Bromide.

The experimental results are summarized in Table I.

Acknowledgment. A grant in support of this study from the Office of Naval Research is gratefully acknowledged.

CHICAGO 14, ILL.

(12) Schard, U. S. 2,557,924, June 26, 1951.

(13) Grundmann and Haldenwanger, *Angew. Chem.*, 62A, 410 (1950).

(14) Microanalyses by Galbraith Microanalytical Laboratories.

[CONTRIBUTION FROM THE RESEARCH LABORATORY, DOMINION RUBBER CO. LTD.]

Macro Rings Containing Carbon, Oxygen and Sulfur

MARSHALL KULKA

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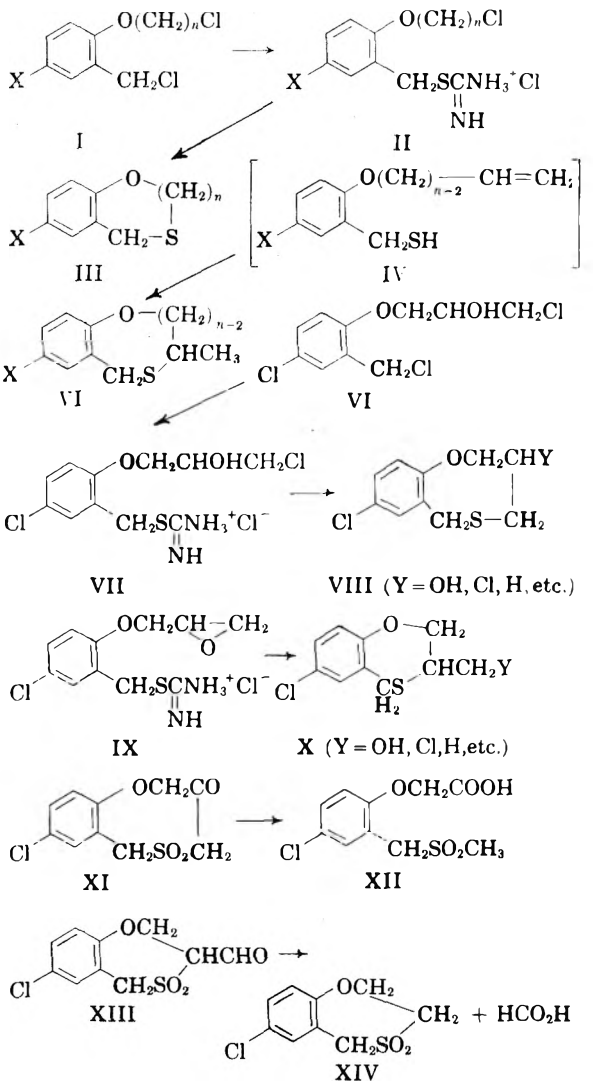
Eight- and nine-membered ring compounds (III) have been synthesized in almost quantitative yields from the corresponding 2-chloroalkoxybenzylisothiuronium chlorides (II). Proof is provided to show that 2-(2-hydroxy-3-chloropropoxy)-5-chlorobenzylisothiuronium chloride (VII) undergoes degradation and cyclization in dilute alkali to form the eight-membered ring compound, namely 3-hydroxy-8-chloro-2,3-dihydrobenzo[g]-1,5-oxathiocin (VIII, Y = OH) and not the seven-membered cyclic compound X.

Recently it was found[1] that *o*-2-chloroethoxybenzylisothiuronium chlorides (II, n = 2) undergo simultaneous degradation and ring closure to form the 2,3-dihydrobenzo(f)-1,4-oxathiepins (III, n = 2) in almost quantitative yields when the principle of high dilution is employed. The remarkable ease with which these seven-membered heterocyclic compounds formed aroused interest in rings of larger size. Therefore *o*-chloropropoxy- (II, n = 3) and *o*-4-chlorobutoxy-(II, n = 4)benzylisothiuronium chlorides were prepared and subjected to the same conditions of cyclization. The larger ring compounds, namely the 2,3-dihydrobenzo(g)-1,5-oxathiocins (III, n = 3) and 2,3,4,5-tetrahydrobenzo-[h]-1,6-oxathionins (III, n = 4) were also obtained in almost quantitative yields. These observations are in harmony with those of Ziegler and Holl[2] who found that macro rings containing one or more hetero atoms are more easily formed than carbocyclic compounds. Apparently the different bond angles of oxygen and sulfur atoms make hetero ring formation easier than carbocyclization.

In this investigation the question of preferred smaller ring formation arose. Thus, under the alkaline conditions of cyclization, might not the isothiuronium salt (II) undergo dehydrochlorination and degradation to form the intermediate alkene (IV) and then cyclize (by addition) to the compound V whose hetero ring is smaller than that of III by one carbon atom?[3] In the case of *o*-2-chloroethoxybenzylisothiuronium chloride (II, n = 2) this possibility of the six-membered ring formation is eliminated on the basis that the smaller ring compound (V, n = 2) obtained from II *via* IV would be a mixed acetal-mercaptal and therefore subject to acid hydrolysis. The compounds obtained from II by cyclization are stable to prolonged boiling with acid, and therefore must possess structure III (n = 2) as postulated previously.[1] With higher homologs of II (n > 2) the route to smaller ring formation exists but it is not the likely one to be followed because dehydrohalogenation of chloroalkyl ethers usually requires conditions more drastic than those used in the present cyclizations. The more probable route is first the conversion of the isothiuronium salt (II) to the *o*-chloroalkoxybenzyl mercaptan {*o*-[Cl(CH$_2$)$_n$O]C$_6$H$_4$CH$_2$SH} which in the presence of alkali cyclizes to III by the chloride-mercaptan reaction. This mechanism is indicated from the study of the ring closure of 2-(2-hydroxy-3-chloropropoxy)-5-chlorobenzylisothiuronium chloride (VII).



(1) Kulka, *Can. J. Chem.*, **33**, 1442 (1955).
(2) Ziegler and Holl, *Ann.*, **528**, 143 (1937).
(3) Poshkus, Armstrong Cork Company, Lancaster, Pa., private communication.

Theoretically 2-(2-hydroxy-3-chloropropoxy)-5-chlorobenzylisothiuronium chloride (VII) which was obtained from the corresponding benzyl chloride (VI) can undergo simultaneous degradation and cyclization in two different ways. Degradation to the mercaptan and then cyclization would yield the eight-membered cycle VIII (Y = OH). On the other hand, VII could be first dehydrochlorinated under the alkaline conditions to form the ethylene oxide IX which then might undergo simultaneous degradation and cyclization to the seven-membered cycle X (Y = OH).

Actually the isothiuronium chloride VII when treated with dilute alkali yielded only one compound. In order to prove that the structure of this compound was VIII (Y = OH) and not the smaller cycle X (Y = OH), attempts were first made to replace the hydroxyl group by hydrogen. The chloro and bromo derivatives VIII (Y = Cl and Br), which were readily obtained from the cyclic alcohol VIII (Y = OH), did not react with magnesium to form the Grignard reagent and the halogens could not be eliminated successfully by reduction with chromous chloride, metal-acid combination or catalytically. Also the cyclic ketosulfone XI, which was obtained by a two step oxidation of VIII (Y = OH), failed to give the required product when subjected to the reduction methods of Wolff-Kishner and Clemmensen.

That the structure of the cyclic alcohol sulfide is VIII (Y = OH) and not X (Y = OH) was finally established in an indirect manner. This compound was first oxidized and then subjected to degradation. It is seen that oxidation of VIII (Y = OH) would lead to the ketosulfone XI while the smaller ring compound X (Y = OH) under the same treatment would produce the ketoaldehyde XIII. It is known that β-ketosulfones of the type XV undergo cleavage in the presence of alkali to form the methylsulfone XVI and an acid salt.[4-6]

$$\underset{\text{XV}}{RSO_2CH_2COR_1} + NaOH \longrightarrow \underset{\text{XVI}}{RSO_2CH_3} + NaOCOR_1$$

Therefore, the cyclic β-ketosulfone XI should cleave in the presence of alkali to form the acid sulfone XII while the β-aldehydrosulfone XIII would give the neutral sulfone XIV and formic acid. Actually when the cyclic carbonyl compound XI or XIII was treated with aqueous alkali the acid sulfone XII was formed in quantitative yield, showing that isothiuronium salt VII undergoes degradation and cyclization to form the eight-membered ring VIII and not the seven-membered ring compound X. This fact adds support to the belief that the larger rings III and not the smaller rings V are formed from the corresponding *o*-chloroalkoxybenzylisothiuronium chlorides (II).

(4) Kulka, *J. Am. Chem. Soc.*, **72**, 1215 (1950).

(5) Otto and Otto, *J. prakt. Chem.*, (2) **36**, 401 (1887).

(6) Ziegler and Connor, *J. Am. Chem. Soc.*, **62**, 1049 (1940).

EXPERIMENTAL[7]

Preparation of the phenoxyalkyl chlorides. These were prepared in 40–60% yields from the phenol and the alkylene dichloride by the same method as was 4-*p*-chlorophenoxybutyl chloride.[8] In each case the higher boiling diphenoxyalkane was the by-product. *4-p-Tolyloxybutyl chloride*[9] boiled at 140–142° (10 mm.). The *1,4-bis-p-tolyloxybutane* melted at 102–103° after crystallization from benzene-methanol.

Anal. Calcd. for $C_{18}H_{22}O_2$: C, 80.00; H, 8.15. Found: C, 80.13, 80.29; H, 8.22, 8.04.

4-p-t-Butylphenoxybutyl chloride distilled at 163–165° (10 mm.) as a colorless liquid, n_D^{24} 1.5100.

Anal. Calcd. for $C_{14}H_{21}ClO$: C, 69.85; H, 8.73. Found: C, 69.95, 69.50; H, 8.56, 8.54.

The residue from the distillation when crystallized from benzene-methanol yielded (11%) white prisms of *1,4-bis-p-t-butylphenoxybutane* melting at 111–112°.

Anal. Calcd. for $C_{24}H_{34}O_2$: C, 81.32; H, 9.60. Found: C, 81.57, 81.20; H, 9.50, 9.60.

3-p-t-Butylphenoxypropyl chloride distilled at 152–153° (10 mm.) as a colorless liquid, n_D^{24} 1.5115.

Anal. Calcd. for $C_{13}H_{19}ClO$: C, 68.87; H, 8.39. Found: C, 69.20, 69.11; H, 8.32, 8.54.

The residual *1,3-bis-p-t-butylphenoxypropane* after crystallization from benzene-methanol melted at 63–64°.

Anal. Calcd. for $C_{23}H_{32}O_2$: C, 81.18; H, 9.41. Found: C, 81.40, 81.46; H, 9.50, 9.34.

3-p-Chlorophenoxypropyl chloride distilled at 141–143° (10 mm.) as a colorless liquid, n_D^{25} 1.5380.

Anal. Calcd. for $C_9H_{10}Cl_2O$: C, 52.68; H, 4.88. Found: C, 53.10, 52.86; H, 5.15, 5.20.

The residual 1,3-bis-*p*-chlorophenoxypropane melted at 121–122° after crystallization from benzene.

Anal. Calcd. for $C_{15}H_{14}Cl_2O_2$: C, 60.60; H, 4.71. Found: C, 60.56, 60.80; H, 4.79, 5.00.

Preparation of o-(chloroalkoxy)benzyl chlorides. 2-(4-Chlorobutoxy)-5-methylbenzyl chloride, 2-(3-chloropropoxy)-5-t-butylbenzyl chloride, and *2-(4-chlorobutoxy)-5-t-butylbenzyl chloride* were prepared in 60–70% yields by the chloromethylation of the corresponding phenyl chloroalkyl ethers using the same procedure as that reported for 2-(2-chloroethoxy)-5-methylbenzyl chloride.[1] These chlorides boiled at 175–180° (10 mm.), 172–175° (10 mm.) and 188–193° (10 mm.), respectively, but pure samples could not be obtained for analyses. The contaminant was the starting phenyl chloroalkyl ether which did not interfere in the next step of the synthesis. *2-(3-Chloropropoxy)-5-chlorobenzyl chloride* and *2-(4-chlorobutoxy)-5-chlorobenzyl chloride* were also prepared by the chloromethylation of the corresponding *p*-chlorophenyl chloroalkyl ether using the same conditions as those reported for the preparation of 2-(2-chloroethoxy)-5-chlorobenzyl chloride.[10] These compounds boiled at 187–190° (10 mm.) and 197–200° (10 mm.), respectively, but again they were contaminated by the small quantities of starting material.

Preparation of the S-o-chloroalkoxybenzyl isothiuronium chlorides (II) (Table I). These were prepared from the benzyl chloride and thiourea by the same method as was used for the preparation of the S-*o*-2-chloroethoxybenzylisothiuronium chloride.[1]

Preparation of the 2,3-dihydroxybenzo[g]-1,5-oxathiocins (III, $n = 3$) *and the 2,3,4,5-tetrahydrobenzo[h]-1,6-oxathionins* (III, $n = 4$) (Table II). These were prepared by gradually adding the aqueous alcoholic solution of the *o*-

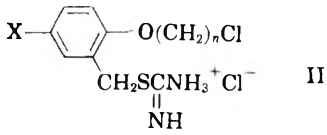
(7) All melting points are corrected.

(8) Kulka, *Can. J. Chem.*, **34**, 1093 (1956).

(9) Genzer, Huttrer and Van Wessem, *J. Am. Chem. Soc.*, **73**, 3159 (1951).

(10) Kulka and Van Stryk, *Can. J. Chem.*, **33**, 1130 (1955).

TABLE I

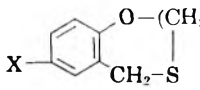


II

Isothiuronium chloride (II)

X	n	M.P., °C.	% Yield	Formula	Analyses Calcd. C	Calcd. H	Found C	Found H
t-Butyl	3	181–183	60	$C_{15}H_{24}Cl_2N_2OS$	51.29	6.82	51.38	6.86
Chloro	3	187–188	26	$C_{11}H_{15}Cl_3N_2OS$	40.06	4.55	40.28	4.44
Methyl	4	168–169	52	$C_{13}H_{20}Cl_2N_2OS$	48.30	6.19	48.51	6.19
t-Butyl	4	167–168	55	$C_{16}H_{26}Cl_2N_2OS$	52.60	7.12	52.92	7.14
Chloro	4	167–168	63	$C_{12}H_{17}Cl_3N_2OS$	41.93	4.95	42.63	5.21

TABLE II

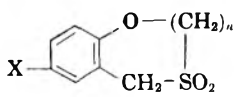


III

Compound III

X	n	M.P., °C. or B.P.	% Yield	Formula	Analyses Calcd. C	Calcd. H	Found C	Found H
t-Butyl	3	B_{11} = 174–175	85	$C_{14}H_{10}OS$	71.19	8.47	70.77	8.38
Chloro	3	46–47	90	$C_{10}H_{11}ClOS$	55.94	5.13	55.99	5.38
Methyl	4	75–76	78	$C_{12}H_{16}OS$	69.23	7.69	69.43	7.83
t-Butyl	4	B_{10} = 185–187	73	$C_{15}H_{22}OS$	72.00	8.80	71.11	8.71
Chloro	4	71–72	83	$C_{11}H_{13}ClOS$	57.77	5.69	58.02	5.75

TABLE III



Sulfone

X	n	M.P., °C.	% Yield	Formula	Analyses Calcd. C	Calcd. H	Found C	Found H
t-Butyl	3	179–178	95	$C_{14}H_{20}O_3S$	62.69	7.46	63.07	7.52
Chloro	3	184–185	90	$C_{10}H_{11}ClO_3S$	48.69	4.46	48.92	4.59
Methyl	4	111–112	90	$C_{12}H_{16}O_3S$	60.00	6.67	60.40	6.70
t-Butyl	4	132–133	78	$C_{15}H_{22}O_3S$	63.83	7.80	63.62	7.73
Chloro	4	168–169	95	$C_{11}H_{13}ClO_3S$	50.67	4.99	50.96	4.94

chloroalkoxybenzylisothiuronium chloride (II) to hot dilute aqueous alkali as previously described.[1]

Preparation of 2,3-dihydrobenzo[g]-1,5-oxathiocin-5,5-dioxides and 2,3,4,5-tetrahydrobenzo[h]-1,6-oxathionin-6,6-dioxides (Table III). The cyclic sulfides III were oxidized to the corresponding sulfones by means of hydrogen peroxide in acetic acid.[1]

2-(2-Hydroxy-3-chloropropoxy)-5-chlorobenzyl chloride (VI). A mixture of acetic acid (600 ml.), paraformaldehyde (21 g.) and zinc chloride (21 g.) was saturated with hydrogen chloride. Then 2-hydroxy-3-chloropropyl p-chlorophenyl ether[11] (100 g.) was added and the resulting solution was heated at 80–90° for 20 hr. About three quarters of the acetic acid was distilled off *in vacuo*. To the residue was added dilute hydrochloric acid, and the precipitated oil was extracted with benzene. The benzene solution was washed with water, with aqueous sodium bicarbonate, and with water. The solvent was removed and the residue distilled, b.p. (10 mm.) 210–215°. This colorless distillate (105 g.) was contaminated with a small quantity of the starting material and thus gave slightly high analytical figures for carbon and hydrogen.

2-[2-Hydroxy-3-chloropropoxy]-5-chlorobenzylisothiuronium chloride (VII). A reaction mixture of the crude benzyl chloride VI (105 g.), thiourea (40 g.) and ethanol (300 ml.) was heated under reflux for 3 hr. The ethanol was removed *in vacuo* and warm water (250 ml.) was added to the residue. The water-insoluble material was extracted with benzene and discarded. The isothiuronium salt VII was very soluble in water and could not be isolated even after concentration

(11) Stephenson, *J. Chem. Soc.*, 1571 (1954).

of the solution. The aqueous solution was therefore used directly in the next experiment.

8-Chloro-3-hydroxy-2,3-dihydrobenzo[g]-1,5-oxathiocin (VIII, Y = OH). The above solution of the isothiuronium salt VII was added dropwise over 2 hr. to a stirred solution of sodium hydroxide (30 g.) in water (1750 ml.) heated on the steam bath. After stirring for an additional one-half hour, the reaction mixture containing precipitated VIII (Y = OH) was cooled and extracted with benzene. The benzene solution was washed with water, the solvent removed, and the residue distilled, b.p. (12 mm.) 210°. The distillate (51 g.) solidified and was crystallized from methanol. The white prisms (42 g. or 50% over-all yield based on the crude benzyl chloride VI) melted at 84–85°.

Anal. Calcd. for $C_{10}H_{11}ClO_2S$: C, 52.07; H, 4.77. Found: C, 51.86; H, 4.86.

8-Chloro-3-hydroxy-2,3-dihydrobenzo[g]-1,5-oxathiocin-5,5-dioxide. The cyclic sulfide VIII (Y = OH) was oxidized with 30% hydrogen peroxide in acetic acid. The white needles which were obtained in 90% yield melted at 191–192°.

Anal. Calcd. for $C_{10}H_{11}ClO_4S$: C, 45.72; H, 4.19. Found: C, 46.13, 46.07; H, 4.43, 4.28.

3-Oxo-8-chloro-2,3-dihydrobenzo[g]-1,5-oxathiocin-5,5-dioxide (XI). 3-Hydroxy-8-chloro-2,3-dihydrobenzo[g]-1,5-oxathiocin-5,5-dioxide (10 g.) was dissolved in acetic acid (100 ml.) at 60° and then chromic oxide (5 g.) was added portionwise with cooling in order to keep the reaction temperature at 60–70°. The resulting solution was heated on the steam bath for 2 hr., then concentrated *in vacuo* to half the original volume. Cold water was added to the residue, the precipitate was filtered, washed with dilute hydrochloric acid and with water, and crystallized from methanol. The white prisms (6.1 g.) melted at 191–192°. This compound was insoluble in aqueous sodium bicarbonate and depressed the melting point of the starting alcohol.

Anal. Calcd. for $C_{10}H_9ClO_4S$: C, 46.07; H, 3.45. Found: C, 46.50, 46.44; H, 3.88, 3.68. The *semicarbazide* of this ketone XI melted at 250° with decomposition.

Anal. Calcd. for $C_{11}H_{12}ClN_3O_4S$: N, 13.22. Found: N, 13.40.

3,8-Dichloro-2,3-dihydrobenzo[g]-1,5-oxathiocin (VIII, Y = Cl). To a solution of 3-hydroxy-8-chloro-2,3-dihydrobenzo-[g]-1,5-oxathiocin (VIII, Y = OH) (10 g.) in benzene (25 ml.) was added thionyl chloride (10 ml.) and the solution was heated under reflux for 2 hr. The solvent and excess thionyl chloride were removed *in vacuo* and the residue which solidified was crystallized from ethanol. The colorless prisms (10 g.) melted at 88–89°.

Anal. Calcd. for $C_{10}H_{10}Cl_2OS$: C, 48.19; H, 4.01. Found: C, 48.54; H, 4.33.

3-Bromo-8-chloro-2,3-dihydrobenzo[g]-1,5-oxathiocin (VIII, Y = Br). To a solution of phosphorus tribromide (5 ml.) in chloroform (10 ml.), 2.2 ml. bromine was added dropwise with cooling. Then VIII (Y = OH) (10 g.) was added portionwise with cooling on a water bath to the reaction mixture containing the precipitated phosphorus pentabromide. The reaction mixture was allowed to stand at room temperature for 0.5 hr. The resulting solution was diluted with chloroform and washed with water, with aqueous sodium hydroxide and again with water. The solvent was removed and the residue was crystallized first from ethanol and then from benzene. The bromide is not very stable in hot ethanol since it liberates hydrogen bromide. The white prisms (9.1 g.) melted at 100–101°.

Anal. Calcd. for $C_{10}H_{10}BrClOS$: C, 40.89; H, 3.41. Found: C, 40.92; H, 3.62.

3-Thiocyanato-8-chloro-2,3-dihydrobenzo[g]-1,5-oxathiocin (VIII, Y = SCN). A solution of 3,8-dichloro-2,3-dihydrobenzo[g]-1,5-oxathiocin (VIII, Y = Cl) (4 g.), sodium thiocyanate (3 g.) and ethanol (100 ml.) was heated under reflux for 2 hr. The precipitated sodium chloride was filtered off and the filtrate taken to dryness *in vacuo*. The residue (4 g.) which solidified on standing was crystallized from methanol. The white prisms melted at 49–50°.

Anal. Calcd. for $C_{11}H_{10}ClNOS_2$: C, 48.62; H, 3.68. Found: C, 48.94; H, 3.57.

3-(N,N-Dimethyldithiocarbamato)-8-chloro-2,3-dihydrobenzo[g]-1,5-oxathiocin [VIII, Y = $S_2CN(CH_3)_2$]. A solution of VIII (Y = Cl) (6 g.), sodium N,N-dimethyldithiocarbamate[8] (6 g.) and acetone (150 ml.) was heated under reflux for 1 hr. The acetone was distilled off, the residue was treated with water and extracted with benzene. The benzene extract was washed with water and the solvent removed. The residue which solidified was crystallized from methanol-benzene, yielding white prisms (6.1 g.) melting at 124–125°.

Anal. Calcd. for $C_{13}H_{16}ClNOS_3$: C, 46.78; H, 4.80. Found: C, 46.80; H, 4.79.

3-Mercapto-8-chloro-2,3-dihydrobenzo[g]-1,5-oxathiocin (VIII, Y = SH). A solution of the dithiocarbamate (VIII, Y = $S_2CN(CH_3)_2$) (3 g.), 85% hydrazine hydrate (10 ml.) and ethanol (75 ml.) was heated under reflux for 40 hr.[8] The solvent was removed *in vacuo*, the residue dissolved in benzene and then washed with dilute hydrochloric acid and with water. The solvent was removed and the residue distilled, b.p. (11 mm.) 220°. The distillate (1.4 g.) solidified and was pulverized and washed with petroleum ether and dried, m.p. 56–57°.

Anal. Calcd. for $C_{10}H_{11}ClOS_2$: C, 48.68; H, 4.46. Found: C, 49.12, 48.94; H, 4.51, 4.38.

2-(Methylsulfonylmethyl)-4-chlorophenoxyacetic acid (XII). To a stirred solution of sodium hydroxide (2 g.) in water (25 ml.) at 40° was added 3-oxo-8-chloro-2,3-dihydrobenzo-[g]-1,5-oxathiocin-5,5-dioxide (XI) (1 g.). The β-ketosulfone XI dissolved in a few minutes. The light yellow solution was heated to 90°, acidified and allowed to cool slowly. The white prisms (1 g.) were filtered, washed, and dried, m.p. 193–194°. This compound depressed the melting point of the starting ketone XI and was soluble in aqueous sodium bicarbonate.

Anal. Calcd. for $C_{10}H_{11}ClO_5S$: C, 43.09; H, 3.95. Found: C, 43.26; H, 4.17.

GUELPH, ONT., CANADA

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

Use of Mixed Carboxylic-Carbonic Anhydrides for Acylations on Carbon and Oxygen[1]

D. STANLEY TARBELL AND JOHN A. PRICE[2]

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Mixed carboxylic-carbonic anhydrides, prepared from carboxylic acids, triethylamine and alkyl chlorocarbonates in an inert solvent at 0°, have been found to acylate diethyl malonate and diethyl ethylmalonate, at room temperature or below, in satisfactory yields. The compounds prepared by this procedure include diethyl benzoylmalonate (V, 68–75%), diethyl acetylmalonate (VI, 54%), diethyl benzoylethylmalonate (VII, 17%) and diethyl (acetylsalicyloyl)-malonate (VIII), identified by conversion to 3-carbethoxy-4-hydroxycoumarin in 45% over-all yield. Benzoic-carbonic anhydride and diethyl cadmium give a 60% yield of propiophenone. Diazoacetophenone and diazomethyl isobutyl ketone are obtained from the corresponding mixed anhydrides and diazomethane. Low yields of 3,4-dimethoxybenzophenone have been obtained from the Friedel-Crafts reaction between the mixed benzoic anhydride and veratrole. This reaction has been shown to involve the mixed anhydride, and not other possible derived compounds, as the reactive intermediate. Phenols have been acylated by the mixed anhydrides. The acylation of alcohols by the mixed anhydrides to form carboxylic esters gives poor yields in general. The mixed anhydride from benzoic acid and 2,4-dimethylpentanol-3 chlorocarbonate yields mainly the benzoate of 2,4-dimethylpentanol-3 in the presence of ethanol and isoamyl alcohol indicating that the mixed anhydride probably undergoes an intramolecular reaction with alkyl-oxygen cleavage of the highly branched alkyl group. The mixed anhydrides appear to be useful reagents for acylation of active methylene groups, of organocadmium compounds, of phenols, of diazomethane, and possibly in some cases of alcohols; the essentially neutral conditions under which they are prepared, and the mild conditions under which they react, may make them the reagent of choice in dealing with acid-sensitive compounds.

In connection with some projected synthetic sequences, we wished to know if the mixed carbonic anhydride procedure,[3] which has proved so useful for the synthesis of amide linkages,[4,5] could be employed for the acylation of malonic esters. The fact that the mixed carboxylic-carbonic anhydrides can be prepared at 0° under essentially neutral conditions, and that they acylate amines under the same mild conditions, made a survey of their reactions with nucleophilic types other than amines a desirable problem. It appears, from the results reported below, that the mixed anhydrides may be used successfully to acylate malonic esters, to prepare ketones from organocadmium compounds, to acylate phenols, and to prepare diazoketones from diazomethane. The use of the mixed anhydrides in the Friedel-Crafts ketone synthesis and in the acylation of alcohols to form carboxylic esters, appears to be less promising as a general synthetic procedure, although both reactions have been shown to take place.

The mixed anhydrides were prepared[3,4] by the action of triethylamine and ethyl chlorocarbonate[6] on the carboxylic acid in ether or preferably in toluene at 0°, according to the following equation

$$\mathrm{RCOOH + ClCOOEt + Et_3N \longrightarrow RCO{-}O{-}CO{-}OEt + Et_3N{:}HCl}$$

I, R = C_6H_5
II, R = CH_3

Most of the acylations of malonic esters were carried out on the magnesium ethoxy derivatives,[7] which are reported[8] to have some advantages over the sodio derivatives.[9] The magnesium ethoxy compounds in dry ether were added, at −5° to 0°, to the mixed anhydride. The mixture was allowed to come to room temperature overnight, and was then worked up. By this procedure, diethyl benzoylmalonate (V) and diethyl acetylmalonate (VI) were obtained, and the hitherto undescribed diethyl benzoylethylmalonate (VII) was prepared in 17% yield.

$$\mathrm{RCOOCOOEt + EtOMgCR'(COOEt)_2 \longrightarrow RCO{-}CR'(COOEt)_2}$$

III, R′ = H
IV, R′ = C_2H_5
V, R = C_6H_5, R′ = H
VI, R = CH_3, R′ = H
VII, R = C_6H_5, R′ = C_2H_5

(1) Part of this material has been presented in a preliminary report [D. S. Tarbell and J. A. Price, *J. Org. Chem.*, 21, 144 (1956)].

(2) Abbott Laboratories Fellow, 1955–56.

(3) J. R. Vaughan, Jr., *J. Am. Chem. Soc.*, **73**, 3547 (1951); R. A. Boissonnas, *Helv. Chim. Acta*, **34**, 874 (1951); T. Wieland and H. Bernhard, *Ann.*, **572**, 190 (1951).

(4) *E.g.*, J. R. Vaughan, Jr., and R. L. Osato, *J. Am. Chem. Soc.*, **73**, 5553 (1951); **74**, 676 (1952); J. R. Vaughan, Jr., and J. A. Eichler, *J. Am. Chem. Soc.*, **75**, 5556 (1953); **76**, 2474 (1954); V. du Vigneaud *et al.*, *J. Am. Chem. Soc.*, **75**, 4879 (1953); **76**, 3107 (1954); B. R. Baker *et al.*, *J. Org. Chem.*, 19, 1786 (1954).

(5) Acylation of thiophenols by the mixed carbonic anhydride procedure is reported by T. Wieland, W. Schäfer, and E. Bokelmann, *Ann.*, **573**, 99 (1951).

(6) Other chlorocarbonates may be used, but the ethyl ester is preferable in working with diethyl malonates, to prevent complications due to ester interchange reactions.

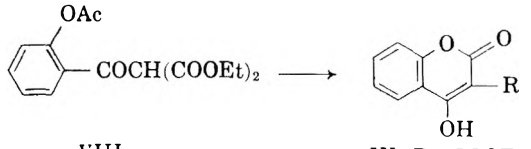
(7) H. Lund, *Ber.*, **67**, 935 (1934); *Org. Syntheses*, **Coll. Vol. II**, 594 (1943).

(8) H. Lund, A. U. Hansen, and A. F. Voigt, *Kgl. Danske Videnskab. Selskab. Mat.-fys. Medd.*, **12**, No. 9 (1933); [*Chem. Abstr.*, **28**, 2333 (1934)].

(9) One trial of sodiomalonic ester and benzoic-carbonic anhydride gave an unsatisfactory yield in our hands; the sodio derivative forms a very viscous solution in ether-toluene, which is not easily manipulated. The magnesium ethoxy derivative is more soluble and is more readily handled, although its preparation is more laborious.

It was not necessary to remove the precipitated triethylamine hydrochloride before the acylation of the malonates; the salt is evidently too insoluble in the reaction mixture to affect the reaction.

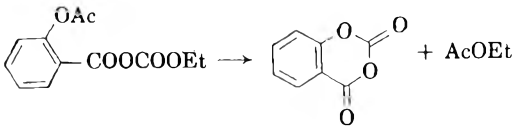
The yield of acylmalonates from a monosubstituted malonic ester by other methods appears to be uniformly low[10,11]; in the present case, there was a considerable forerun, which appeared, from its analysis and infrared spectrum, to be a mixture of starting material and some of the possible cleavage products.[12] The acylalkylmalonate VII was cleaved to benzoic acid by standing for several months at room temperature; both V and VII were split rapidly by phenylhydrazine, giving β-benzoylphenylhydrazine. This high rate of cleavage of the acyl group is in accord with previous experience.[10,13] The attempted acylation of III by the mixed anhydride prepared from salicylic acid was unsatisfactory; there appeared to be some dimer formed,[14] because heating the anhydride or hydrolysis with water did not regenerate all of the salicylic acid. However, acetylsalicylic acid was converted to the mixed anhydride and was allowed to react with the enolate III in the usual way; the product, presumably VIII, cyclized to



VIII

IX, R = COOEt
X, R = H

3-carbethoxy-4-hydroxycoumarin on distillation.[15] The conversion was also brought about, in 45% over-all yield from acetylsalicylic acid, by 10% alkali in the cold. The carbethoxycoumarin IX was hydrolyzed and decarboxylated to yield 4-hydroxycoumarin (X); IX was identified by mixed melting point with an authentic sample of this compound,[16] and X was condensed with formaldehyde to yield 3,3′-methylenebis(4-hydroxycoumarin).[17] A possible intermediate in the acylation by the mixed anhydride from acetylsalicylic acid (XI) would be the

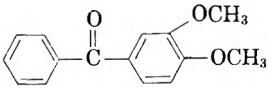


XI XII

cyclic anhydride XII[18]; this compound was prepared, and it did not acylate the malonate derivative in yields at all comparable to those obtained with the mixed anhydride XI. This observation, as well as those of Ghosh,[15] indicate that XII is not an intermediate in the acylation.

It was found that the benzoic-carbonic anhydride I and diethyl cadmium[19] gave a 60% yield of propiophenone; presumably this reaction is general. In the reaction of the mixed anhydride with the diethyl cadmium, it is necessary to remove the triethylamine hydrochloride from the mixed anhydride by filtration, before the mixed anhydride is added to the dialkyl cadmium solution. If this is not done, the amine salt appears to decompose the cadmium compound more rapidly than the mixed anhydride reacts with the cadmium compound, and no ketone is obtained.

Davies[18] showed that the cyclic anhydride XII, and the corresponding one derived from glycolic acid, gave good yields in the Friedel-Crafts reaction with benzene and aluminum chloride. We have obtained a maximum of 17% of 3,4-dimethoxybenzophenone (XIII) by the action of the benzoic-carbonic anhydride I on veratrole with aluminum



XIII

chloride at 0° with carbon disulfide as solvent. With stannic chloride as catalyst, 11% of the ketone was obtained. Treatment of veratrole with the mixed anhydride I and perchloric acid[20] yielded no ketone.

It was possible that the ketone XIII actually obtained in the acylations using the benzoic-carbonic anhydride I might have been due to the intermediate formation, from the mixed anhydride, of ethyl benzoate, benzoic acid, or benzoic anhydride, which then acted as acylating agents. However, separate trials of each of these three compounds under the conditions used for the mixed anhydride acylations, failed to yield detectable amounts of

(10) R. Meyer and H. Lüders, *Ann.*, **415**, 43 (1918).

(11) W. S. Johnson and R. D. Offenhauer, *J. Am. Chem. Soc.*, **67**, 1045 (1945); H. G. Walker and C. R. Hauser, *J. Am. Chem. Soc.*, **68**, 1386 (1946).

(12) *Cf.* A. C. Cope and S. M. McElvain, *J. Am. Chem. Soc.*, **54**, 4311 (1932) for the cleavage of malonates by sodium ethoxide.

(13) W. Borsche and U. Wannagat, *Ber.*, **85**, 193 (1952).

(14) *Cf.* W. Baker, W. D. Ollis, and T. S. Zealley, *J. Chem. Soc.*, 201 (1951).

(15) K. C. Ghosh, *J. Indian Chem. Soc.*, **24**, 321 (1947), reported that acetylsalicyloyl chloride and methylmalonic ester yield o-$C_6H_4(OAc)COC(CH_3)(COOEt)_2$ which distills at 198° (4 mm.); it was cyclized to 3-methyl-4-hydroxycoumarin by dilute sulfuric acid.

(16) M. E. Hultquist, U. S. Patent **2,449,038** [*C. A.*, **43**, 693 (1949)]; R. Anschutz, *Ann.*, **367**, 174 (1909).

(17) M. A. Stahmann, C. F. Huebner, and K. P. Link, *J. Biol. Chem.*, **138**, 513 (1941).

(18) L. A. Dupont, French Patent **771,653** [*C. A.*, **29**, 816 (1935)]; A. E. Chichibabin, *Compt. rend.*, **213**, 355 (1941); W. H. Davies, *J. Chem. Soc.*, 1357 (1951).

(19) H. Gilman and J. F. Nelson, *Rec. trav. chim.*, **55**, 518 (1936); for reviews of the preparation of ketones from acid chlorides and organometallic compounds, see J. Cason, *Chem. Revs.*, **40**, 15 (1947); D. A. Shirley, *Org. Reactions*, VIII, 28–58 (1954).

(20) H. Burton and P. F. G. Praill, *J. Chem. Soc.*, 529 (1951), obtained Friedel-Crafts acylations with carboxylic anhydrides and aqueous perchloric acid as catalyst.

the ketone. Hence it appears that the mixed anhydride is the acylating agent.

Attempts to acylate furan with the mixed anhydride I and an iodine catalyst[21] were unsuccessful. The reaction of benzoic-carbonic anhydride with ethereal diazomethane yielded a small amount of pure diazoacetophenone; the low yield apparently due to difficulties in isolation of the low melting solid. The action of diazomethane on the mixed isovaleric-carbonic anhydride, $(CH_3)_2CHCH_2COOCOOEt$, gave a 57% yield of the corresponding diazoketone. This reaction should be useful synthetically. In these reactions, the triethylamine hydrochloride was separated before the addition to diazomethane.

The usefulness of the mixed anhydrides for acylation of phenols and alcohols was investigated in several cases. The benzoylation of phenol by the benzoic-carbonic anhydride I have a poor yield of the low-melting phenyl benzoate; 4-phenylphenyl benzoate was obtained in 54% yield of recrystallized material from 4-phenylphenol. Benzyl benzoate was obtained in 47% yield from the benzoic-carbonic anhydride I and benzyl alcohol.

Benzoylation of isoamyl alcohol by the anhydride I gave 25% of isoamyl benzoate, and there was some evidence for the formation of benzoic anhydride and ethyl benzoate. The reaction involved in the acylation of an alcohol by the anhydride I would be

$$C_6H_5\overset{O}{\overset{\|}{C}}OCOC_2H_5 + ROH \longrightarrow C_6H_5\overset{O}{\overset{\|}{C}}OR + CO_2 + C_2H_5OH$$

The C_2H_5OH liberated might react with unchanged mixed anhydride in several ways, some of which follow

$$C_6H_5\overset{O}{\overset{\|}{C}}OCOC_2H_5 + C_2H_5OH \longrightarrow C_6H_5COOC_2H_5 + CO_2 + C_2H_5OH$$

$$C_6H_5\overset{O}{\overset{\|}{C}}OCOC_2H_5 + C_2H_5OH \longrightarrow C_6H_5COOH + C_2H_5O\overset{O}{\overset{\|}{C}}OC_2H_5$$

$$C_6H_5\overset{O}{\overset{\|}{C}}OCOC_2H_5 + C_6H_5COOH \longrightarrow (C_6H_5CO)_2O + CO_2 + C_2H_5OH$$

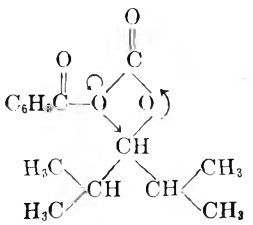
It seemed that these unwanted side reactions might be prevented by using as the alcohol component of the mixed anhydride a highly branched alcohol such as 2,4-dimethylpentanol-3 (XIV). It is known from the work of Norris[22] that the rate of acylation of alcohols is decreased greatly by increasing substitution, and one might predict that XIV would react with acylating agents at a rate smaller than that of ethanol by a factor of at least 10^2.

$$(CH_3)_2CH\underset{\displaystyle OR}{\underset{|}{C}}HCH(CH_3)_2$$

XIV, R = H
XV, R = COCl
XVI, R = $CONH_2$
XVII, R = C_6H_5CO

2,4-Dimethylpentanol-3 was prepared readily by lithium aluminum hydride reduction of diisopropyl ketone,[23] and was converted to the chlorocarbonate XV by phosgene; this compound was also characterized as the solid carbamate XVI.

The mixed benzoic-carbonic anhydride prepared from the highly branched chlorocarbonate XV was treated with ethyl alcohol; the products were ethyl benzoate (13%) and 2,4-dimethylpentanol-3 benzoate (XVII, 49%). It is highly unlikely that this ester can have resulted from reaction of the liberated dimethylpentanol with unchanged anhydride, in competition with ethanol; it seems probable that the branched chain ester results from an intramolecular reaction of the S_Ni type, with the transition state shown below, involving alkyl-oxygen cleavage. Examination of models shows that this four membered cyclic transition state is possible on steric grounds. This reaction is being investigated further.



The mixed anhydride procedure does not therefore appear at present to be a promising one for the acylation of alcoholic hydroxyl groups.

EXPERIMENTAL[24]

DIETHYL BENZOYLMALONATE (V)

A. Magnesium ethoxy malonic ester.[7,25] Magnesium turnings (5.0 g.), 5 cc. of commercial absolute alcohol, 0.2 cc. of carbon tetrachloride, and 6 cc. of a mixture of 32.0 g

(21) *Cf.* H. D. Hartough and A. I. Kosak, *J. Am. Chem. Soc.*, 68, 2639 (1946).

(22) J. F. Norris and A. A. Ashdown, *J. Am. Chem. Soc.*, 47, 837 (1925); J. F. Norris and F. Cortese, *J. Am. Chem. Soc.*, 49, 2640 (1927).

(23) J. B. Conant and A. H. Blatt, *J. Am. Chem. Soc.*, 51, 1227 (1929), showed that this ketone was reduced to the secondary alcohol by Grignard reagents.

(24) Analyses are by Miss Annette Smith and Microtech Laboratories. Yields are based on starting material taken and do not take into account any recovered starting material.

(25) *Cf.* G. A. Reynolds and C. R. Hauser, *Org. Syntheses*, 30, 70 (1950).

of diethyl malonate (redistilled n_D^{25} 1.4047) and 16 cc. of absolute alcohol are placed in a flask equipped with a dropping funnel and a reflux condenser protected by a calcium chloride tube. The reaction starts spontaneously and may require occasional cooling; the remainder of the diethyl malonate is added at a rate sufficient to maintain a vigorous reaction. When the reaction has cooled to room temperature, 60 cc. of dry ether is added cautiously; the ether dissolves the cake of magnesium ethoxy derivative, and a vigorous reaction starts with unchanged magnesium. When the reaction has subsided, the mixture is heated on the steam bath until nearly all of the magnesium has dissolved; this requires 6–8 hr. The alcohol and ether are removed by distillation first at atmospheric pressure, then with the water pump. Dry benzene (60 cc.) is added to the residue, and the solvent is then removed as before. The residue is dissolved in 60 cc. of dry ether.

B. Benzoic-carbonic anhydride (I). A solution of 24.4 g. of benzoic acid and 20.2 g. of triethylamine in 200 cc. of dry toluene is placed in a three-necked flask fitted with a stirrer, a low temperature thermometer, and a dropping funnel protected by a drying tube. The solution is cooled below 0° with an ice-salt mixture, and 21.7 g. of redistilled ethyl chlorocarbonate is added at such a rate that the temperature does not rise above 0°; this requires 25–30 min. Triethylamine hydrochloride precipitates during both the addition and a subsequent period of stirring for 15–25 min.

C. Acylation reaction. The dropping funnel used for the chlorocarbonate addition is replaced by another containing the ethereal solution of the ethoxy magnesium malonate. The ether solution is added to the mixed anhydride with stirring, keeping the temperature at −5°–0°. The mixture is allowed to stand overnight and to come to room temperature during this time. It is then treated with 400 cc. of approximately 2*N* sulfuric acid, the layers are separated, the aqueous solution is extracted once with ether, and the organic layers are combined. They are washed once with 2*N* sulfuric acid, and then with concentrated bicarbonate solution until no further benzoic acid is obtained on acidification of the bicarbonate extracts. If the benzoic acid is not all removed at this stage, it is troublesome during the distillation. The organic layer is washed with water, dried, the solvent is removed, and the residue distilled through a column. The yield of material of b.p. 144–149° (0.8 mm.) is 35.8–39.4 g. (68–75%), n_D^{20} 1.5097. It gives a red color with ferric chloride and its infrared spectrum shows bands, among others, at 1739, 1684, and 1600 cm.$^{-1}$ It gives an ethylamine salt, m.p. 90–92°, as reported,[26] and the copper derivative melts[27] at 182°; treatment with phenylhydrazine in glacial acetic acid gives β-benzoylphenylhydrazine,[10,13] m.p. 169–170°, undepressed when mixed with an authentic sample.[28]

Diethyl benzoylethylmalonate (VII). The magnesium ethoxy enolate was prepared as described above from 37.6 g. of diethyl ethylmalonate. The mixed anhydride was prepared as above from 26.8 g. of benzoic acid, 20.2 g. of triethylamine, and 27.2 g. of isobutyl chlorocarbonate in 400 cc. of toluene. The enolate was added to the mixed anhydride over a 30-min. period at 0°; the mixture was allowed to come to room temperature, was stirred for 2 hr. and was then heated at 50° for 30 min. The mixture was worked up as described above; acidification of the bicarbonate washes yielded 10 g. of benzoic acid. The product was distilled twice, the first distillation yielding a large forerun, and a fraction of 3.49 g., b.p. 125–130° (0.3 mm.), n_D^{20} 1.5020.

Anal. (on a redistilled sample, b.p. 126–127° (0.3 mm.), n_D^{20} 1.5021). Calcd. for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.40; H, 6.84.

The forerun was distilled through a spinning band column, and an additional fraction of 6.47 g., b.p. 102–108° (0.05 mm.), n_D^{20} 1.4997. The combined yield, 9.96 g. is 17%. The compound deposited benzoic acid after standing for several months, and was cleaved by phenylhydrazine to form benzoylphenylhydrazine. The infrared spectrum in the double bond region showed bands at 1724, 1684, 1592, and 1575 cm.$^{-1}$

Diethyl acetylmalonate (VI). This was prepared by the procedure described for diethyl benzoylmalonate. The reaction was run on a 0.2 mole scale, and yielded 12.1 g. of product, b.p. 110–115° (13 mm.), n_D^{20} 1.4464 and 5.72 g., b.p. 115–117° (13 mm.), n_D^{20} 1.4477.

The forerun was redistilled and yielded 3.78 g., b.p. 108–111° (12 mm.), n_D^{20} 1.4471. The combined yield, 21.63 g. was 53.5%. The dinitrophenylhydrazone melted at 146–148°; Lund[8] reported 147°.

3-CARBETHOXY-4-HYDROXYCOUMARIN (IX)

A. By acylation of malonic ester with the mixed anhydride from acetylsalicylic acid. The mixed anhydride was prepared from 39.6 g. (0.22 mole) of acetylsalicylic acid, 20.2 g. (0.2 mole) of triethylamine, and 21.7 g. (0.2 mole) of ethyl chlorocarbonate in 250 cc. of dry toluene, as described above for I. To this anhydride was added the magnesium ethoxy enolate in ether prepared as above from 0.2 mole of malonic ester. The temperature was kept at 0° during the addition, which required about 45 min. The reaction mixture was then allowed to come to room temperature by standing overnight, was treated with 400 cc. of cold 5% sulfuric acid, the organic layer was separated, the aqueous layer was extracted with two portions of ether, and the extracts were added to the organic layer. The combined organic solutions were washed with dilute sulfuric acid, with water, and three times with saturated sodium bicarbonate solution. The solution was dried, and the solvent was removed at atmospheric pressure, and finally *in vacuo*.

The yellow residual oil (40 g.) was stirred with 10% sodium hydroxide at room temperature until the white sodium salt of IX had precipitated completely and the oil had disappeared. The salt was collected by filtration, and acidification of the filtrate yielded 1 g. of impure 3-carbethoxy-4-hydroxycoumarin (IX). The sodium salt was dissolved in hot water, cooled slightly, and acidified carefully with dilute sulfuric acid. The precipitated product weighed 24.5 g., was combined with the above 1 g. from the filtrate, and was recrystallized from ethanol; the product (21.1 g., 45%) melted at 99–101°. Anschutz[16] reported 101°. It showed no depression on mixed melting point with an authentic sample of IX prepared as described by Hultquist.[16]

4-Hydroxycoumarin (X).[16] Hydrolysis of 1.28 g. of the 3-carbethoxy-4-hydroxycoumarin prepared by the mixed anhydride procedure by refluxing with 10% aqueous potassium hydroxide for 8 hr. yielded, after acidification and two crystallizations of the product from water, 4-hydroxycoumarin, m.p. 209–210°. The reported[17] melting point is 210°.

The compound was further characterized by condensation with formaldehyde to 3,3′-methylene-bis(4-hydroxycoumarin), melting point after crystallization from cyclohexanone, 279–281°; the reported[17] melting point is 288–289°.

Acylation of malonic ester by the cyclic carbonic anhydride from salicylic acid (XII). The cyclic anhydride XII was prepared by W. H. Davies' procedure,[18] and melted at 112–118° with decomposition; Davies reported 113–121°. The compound yielded *o*-hydroxybenzophenone when treated with benzene and aluminum chloride, as reported.[18]

The magnesium ethoxy malonic ester was prepared from 0.1 mole of reagents as described previously; it was added dropwise to 16.4 g. (0.1 mole) of the cyclic anhydride (XII) in 175 cc. of dry ether. The reaction mixture was surrounded by an ice bath so that the temperature remained at 0° or

(26) F. E. King, T. J. King, and G. B. Thompson, *J. Chem. Soc.*, 552 (1948).

(27) H. Bernhard, *Ann.*, 282, 166 (1894), reported 180°.

(28) E. Fischer, *Ann.*, 190, 125 (1878).

below during this addition. It was stirred for 4 hr. at 0° and then allowed to reach room temperature on overnight standing. The mixture was decomposed with 200 cc. of sulfuric acid (*ca.* 2*N*) and 20 g. of ice. The aqueous layer was separated and washed twice with ether. The ether layers were combined and washed successively with dilute sulfuric acid, water, saturated sodium bicarbonate solution, and finally with water. Acidification of the bicarbonate washes yielded 13.39 g. of impure salicylic acid.

The organic layer was dried, the ether was removed, and the residue was treated with 10% sodium hydroxide as described above. A small amount of salt precipitated. It was filtered off, was dissolved in water, and the aqueous solution was acidified. Less than a gram of material was obtained, m.p. 100–102° after recrystallization from aqueous ethanol. A mixed melting point with an authentic sample of 3-carbethoxy-4-hydroxycoumarin (IX) remained at 101–102°.

Propiophenone from diethyl cadmium and benzoic-carbonic anhydride (I). Diethyl cadmium was prepared in the usual way[19] from ethylmagnesium bromide (from 0.2 mole of ethyl bromide and magnesium) and 19.6 g. (0.11 mole) of cadmium chloride; the ether solution was refluxed on the steam bath for 30 min. to complete the reaction, at which time there was a negative Gilman reaction for Grignard reagent.

The mixed anhydride was prepared as usual from 19.5 g. (0.16 mole) of benzoic acid, 16.2 g. of triethylamine, and 17.4 g. of ethyl chlorocarbonate. The solution was separated from the precipitated triethylamine hydrochloride by sucking it out through a filter stick inserted into the bottom of the flask. (When the hydrochloride was not removed, no propiophenone resulted from the reaction.) The solution was transferred directly into a cold jacketed dropping funnel without exposure to the atmosphere. The hydrochloride was washed with two fresh 30 cc. portions of dry toluene, and the washes were combined with the above solution.

The solution of the anhydride was added to the cadmium compound with stirring, over a period of 1 hr., keeping the temperature below 2°. The mixture was allowed to come to room temperature overnight. The cake which formed was partially broken up by heating at reflux for 2 hr. The mixture was cooled and decomposed with 200 g. of ice and water followed by the addition of 50 cc. of 20% sulfuric acid. The aqueous layer was separated and washed with two 50-cc. portions of ether, the combined ether layers were washed with 20% sulfuric acid, once with water, and three times with 100-cc. portions of 5% bicarbonate solution. The third bicarbonate wash gave no benzoic acid on acidification; the first two yielded 0.95 g. of benzoic acid.

The organic layer was washed once with water, twice with saturated sodium chloride solution, was dried, the solvent was removed, and the residue was distilled. Three fractions were collected in the range 87–103° (17 mm.), n_D^{20} 1.5251, 1.5274, and 1.5263;[29] the combined fractions weighed 13.0 g. (61%). The semicarbazone melted at 173–174°, and gave no depression on mixed melting point with an authentic sample.

Acylation of veratrole by benzoic-carbonic anhydride; 3,4-dimethoxybenzophenone (XIII). The mixed anhydride was prepared from 3.05 g. of benzoic acid, 2.5 g. of triethylamine, and 2.7 g. of ethyl chlorocarbonate in 40 cc. of carbon disulfide at 0°. After stirring for 15 min., 6.9 g. of powdered aluminum chloride was added over a period of 5 min. After stirring for 5 min., a solution of 3.46 g. of veratrole in 10 cc. of carbon disulfide was added over a 15-min. period. The mixture became green, and was allowed to come to room temperature overnight. Ice water was then added to decompose the mixture, the layers were separated, the flask was washed with 25 cc. of chloroform, and the aqueous layer was washed with 25 cc. of chloroform and 25 cc. of ether. The combined organic layers were washed with two 50-cc. portions of 5% bicarbonate; these washes yielded only 0.25 g. of benzoic acid on acidification. The organic layer was dried, and was concentrated to a yellow oil by passing air over it at 50°. The oil slowly crystallized, and from it was obtained after three crystallizations from dilute ethanol 1.02 g. (17%) of 3,4-dimethoxybenzophenone, m.p. 100.5–101.5°, which showed no depression on mixed melting point with an authentic sample.[30]

The mixed anhydride (0.08 mole), prepared in benzene-ethylene chloride, was freed from triethylamine hydrochloride with a filter stick, was added to 0.073 mole of veratrole, and 0.22 mole of stannic chloride was added. The reaction was carried out essentially as above, and yielded 1.92 g. (11%) of recrystallized dimethoxybenzophenone.

Attempted acylation of veratrole with ethyl benzoate, with benzoic acid and with benzoic anhydride, using aluminum chloride and the conditions described above, gave no isolatable amount of the dimethoxybenzophenone. In the benzoic anhydride run, the noncrystalline oil was distilled, and appeared, from its refractive index and infrared spectrum, to be a mixture of veratrole and benzoyl chloride.

Isobutyl diazomethyl ketone. A solution of the mixed isovaleric-carbonic anhydride was prepared in 175 cc. of dry ether from 0.1 mole of reagents. The anhydride solution was separated from the triethylamine hydrochloride by filtration with a filter stick, the hydrochloride was washed with 50 cc. of cold ether which was combined with the other solution; the anhydride solution was added to an ethereal diazomethane solution prepared from 20.6 g. (0.2 mole) of nitrosomethylurea. After standing 1 hr. at 0° the mixture was allowed to reach room temperature overnight. The ether was removed with an aspirator at 40°, and the dark residue yielded upon distillation 7.2 g. of isobutyl diazomethyl ketone,[31] b.p. 80–100° (18 mm.). The material showed a very strong band at 2085 cm.$^{-1}$, which is characteristic of diazoketones.[32]

The yield of diazoketone was not improved by using 4 moles of diazomethane per mole of anhydride, instead of two as above.

Diazoacetophenone was prepared by the above procedure, and was isolated by crystallization; the yield of twice recrystallized material,[33] m.p. 49–50°, was 7%.

4-Phenylphenyl benzoate. 4-Phenylphenol (17.0 g.) in 120 cc. of ether and 30 cc. of chloroform was added at 0° to a solution of the mixed benzoic-carbonic anhydride prepared from 0.1 mole of reagents in 100 cc. of toluene. The mixture was allowed to come to room temperature overnight, was then heated to 40°, and quickly cooled in an ice bath. The mixture was shaken with water, more toluene was added to dissolve the remaining solid, and the organic layer was washed with saturated bicarbonate, which removed no benzoic acid, and then with 5% sodium hydroxide solution, which removed 3.48 g. of 4-phenylphenol, m.p. 164.5–166°. From the organic layer was obtained a solid, which, after crystallization from alcohol, yielded 14.6 g. (53%) of 4-phenylphenyl benzoate, m.p. 149–150.5°; the reported value[34] is 150°.

Benzyl benzoate. This ester was obtained in 47% yield by addition of an equivalent amount of benzyl alcohol to the benzoic-carbonic anhydride.

Isoamyl benzoate was obtained in 25% yield in a similar manner, from a 0.1 mole run, except that there was an excess of 0.05 mole of triethylamine present over the amount

(29) O. Wallach, *Ann.*, **332**, 317 (1904), reports n_D^{20} 1.5270.

(30) F. Brüggemann, *J. prakt. Chem.*, **53**, 253 (1896), reported a melting point of 99°.

(31) L. Birkofer, *Ber.*, **80**, 88 (1947).

(32) K. B. Wiberg and T. W. Hutton, *J. Am. Chem. Soc.*, **76**, 5367 (1954).

(33) L. Wolff, *Ann.*, **325**, 142 (1902) reported the same melting point.

(34) J. Kaiser, *Ann.*, **257**, 101 (1890).

necessary to neutralize the hydrogen chloride formed in the mixed anhydride preparation.

2,4-Dimethylpentanol-3 (XIV). 2,4-Dimethylpentanone-3 (86.6 g., b.p. 122–124°, n_D^{25} 1.3981) was added over a period of 1 hr. to a suspension of 8.36 g. of lithium aluminum hydride in 300 cc. of dry ether. The mixture was then refluxed 1 hr., water was added cautiously dropwise until gas evolution ceased, and the reaction mixture was poured into 150 cc. of ice water, to which was added 600 cc. of 10% sulfuric acid solution. The aqueous solution was extracted twice with ether, the ether was washed with water until neutral, was dried, and the solvent was removed. Distillation yielded 66.0 g. (75%) of product,[35] b.p. 133–137°, n_D^{20} 1.4235. The phenylurethan melted at 92.5–94.5°; Conant and Blatt[23] reported 95°.

2,4-Dimethylpentanol-3 chlorocarbonate (XV). In a 250 cc. three-necked flask cooled in a dry ice–acetone bath was condensed 93.0 g. (0.95 mole) of phosgene. The flask was transferred to an ice bath, fitted with a stirrer, a condenser with an outlet tube leading to a drain, and a dropping funnel. The alcohol XIV (76 g., 0.66 mole) was added over a period of 45 min. The ice bath was removed and the mixture was allowed to stand at room temperature overnight. The excess phosgene was removed by an aspirator over a period of 90 min. Distillation at 60–70 mm. yielded material, b.p. 76–90°, n_D^{20} 1.4218–1.4220, which was a mixture of chlorocarbonate and starting material, because it showed absorption at 3330 and 1773 cm.$^{-1}$ Further distillation yielded two fractions, b.p. 90–100°, n_D^{20} 1.4225, and b.p. 99° (n_D^{20} 1.4235). These two fractions weighed 40 g., which is a 34% yield of chlorocarbonate; they showed no absorption at 3330 cm.$^{-1}$; but did have the band at 1773 cm.$^{-1}$

Anal. (sample with n_D^{20} 1.4235). Calcd. for $C_8H_{15}ClO_2$: C, 53.77; H, 8.48. Found: C, 53.62; H, 8.39.

(35) These agree with the reported values (G. Poletaeff, *Ber.*, **24**, 1309 (1891).

2,4-Dimethylpentanol-3 carbamate (XVI). The chlorocarbonate (1.0 g., n_D^{20} 1.4225) dissolved in 10 cc. of ether at 5° was treated with 15 cc. of concentrated aqueous ammonia; the ether layer was decanted, and the aqueous layer was extracted twice with ether. The white residue obtained from the combined ether layers gave, after two crystallizations from benzene, material of m.p. 124–124.8°. The melting point was raised to 125.2–126.2° by vacuum sublimation.

Anal. Calcd. for $C_8H_{17}NO_2$: C, 60.34; H, 10.76; N, 8.80. Found: C, 60.59; H, 11.00; N, 8.76.

Action of benzoic-2,4-dimethylpentanol-3 carbonic anhydride on ethanol. A solution of the benzoic-carbonic anhydride was prepared in 50 cc. of toluene from 0.05 mole of benzoic acid, triethylamine, and 2,4-dimethylpentanol-3 chlorocarbonate. After this mixture had been stirred at 0° for 20 min., 2.3 g. of absolute ethyl alcohol was added. The mixture was allowed to come to room temperature overnight. The triethylamine hydrochloride was filtered off, washed with toluene, and the combined toluene solutions were washed with saturated bicarbonate. No benzoic acid was obtained on acidification. The toluene solution was washed with water, dried, and the solvent was removed. The residue on distillation yielded 1.57 g. (20%) of material, b.p. 97–102° (21 mm.) which was mainly ethyl benzoate. The fractions (6.31 g., 57%), b.p. 145–155° (22 mm.) n_D^{26} 1.4828–1.4872, were shown to be 2,4-dimethylpentanol-3 benzoate[36] by saponification to benzoic acid and 2,4-dimethylpentanol-3, which was identified through the crystalline phenylurethan.

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(36) G. Vavon, M. Barbier, G. Thiebaut, *Bull. soc. chim. France*, [5] **1**, 812 (1934), report the following properties for this ester: b.p. 141–142° (15 mm.); n_D^{19} 1.4916.

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF IOWA STATE COLLEGE]

Organotin Compounds: Cyclopentadienyl and Related Derivatives

HENRY GILMAN AND LEWIS A. GIST, JR.

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Triphenyl-1-cyclopentadienyltin, diphenyldi-1-cyclopentadienyltin, phenyltri-1-cyclopentadienyltin, and diphenyldi-1-indenyltin were prepared. Cyclopentadienyl derivatives of tin are unstable in the presence of air and light. Triphenyl-1-cyclopentadienyltin is readily hydrolyzed by water and is cleaved by bromine and by *n*-butyllithium to yield bis-(triphenyltin)oxide, triphenyltin bromide, and tetraphenyltin, respectively. Triphenyl-1-indenyltin and diphenyldi-1-indenyltin were not hydrolyzed under analogous conditions. Addition products were obtained from the Diels-Alder reaction of triphenyl-1-cyclopentadienyltin with maleic anhydride, with diethyl maleate, and with diethyl acetylenedicarboxylate. Triphenyl-2-furyltin did not react with maleic anhydride under corresponding conditions.

Organometallic compounds containing the cyclopentadienyl group have been reported frequently. The recent interest in metallic derivatives of cyclopentadiene, however, has been centered primarily around the preparation and the properties of bis-(cyclopentadienyl)iron (ferrocene)[1–5] and analogous derivatives[6–11]; and the information accumulated in this area has been reviewed.[12] Very little is known about cyclopentadienyl derivatives of the Group IV-B metals. Organotin compounds of this

(1) Wilkinson, Rosenblum, Whiting, and Woodward, *J. Am. Chem. Soc.*, **74**, 2125 (1952).
(2) Woodward, Rosenblum, and Whiting, *J. Am. Chem. Soc.*, **74**, 3458 (1952).
(3) Jaffe, *J. Chem. Phys.*, **21**, 156 (1953).
(4) Pauson, *J. Am. Chem. Soc.*, **76**, 2187 (1954).
(5) Broadhead and Pauson, *J. Chem. Soc.*, 367 (1955).
(6) Wilkinson, *J. Am. Chem. Soc.*, **74**, 6146 (1952).
(7) Fischer and Jara, *Z. Naturforschung*, 8B, 217 (1953).
(8) Wilkinson, Pauson, Birmingham, and Cotton, *J. Am. Chem. Soc.*, **75**, 1011 (1953).
(9) Wilkinson, Pauson, and Cotton, *J. Am. Chem. Soc.*, **76**, 1970 (1954).
(10) Summers, *J. Am. Chem. Soc.*, **76**, 2278 (1954).
(11) Wilkinson, *J. Am. Chem. Soc.*, **76**, 209 (1954).
(12) Fischer, *Angew. Chem.*, **67**, 475 (1955); see also Cotton, *Chem. Revs.*, **55**, 551 (1955).

type, for example, were mentioned very briefly in a patent,[13] but no specific compounds were included in the reference.[14]

This report is concerned with the preparation and the properties of some organotin compounds containing the cyclopentadienyl and the indenyl groups. In addition, the Diels-Alder reaction has been investigated between triphenyl-1-cyclopentadienyltin (I), on the one hand, and maleic anhydride, diethyl maleate, and diethyl acetylenedicarboxylate, on the other, and the results obtained have been included herein.

Cyclopentadienylmagnesium bromide was prepared by a previously described procedure,[15,16] then treated with the appropriate organotin chloride to obtain triphenyl-1-cyclopentadienyltin (I), diphenyldi-1-cyclopentadienyltin (II), and phenyltri-1-cyclopentadienyltin (III). The preparation of tetra-1-cyclopentadienyltin (IV) was also attempted, but the isolation of this derivative proved to be somewhat troublesome, and the product obtained decomposed before it was completely characterized. The following equations are illustrative of the method used for the preparation of these derivatives:

$$C_2H_5MgBr + C_5H_6 \xrightarrow{\text{(benzene-ether)}} C_5H_5MgBr + C_2H_6$$

$$y(C_5H_5MgBr) + (C_6H_5)_{4-y}SnCl_y \longrightarrow (C_6H_5)_{4-y}Sn(C_6H_5)_y + y(MgBrCl)$$

(I), (II), (III), and (IV)

Incidental to this investigation, it was observed that cyclopentadienylmagnesium bromide did not give a positive Color Test I, when this test was taken in the conventional manner.[17] This apparently anomalous behavior of cyclopentadienylmagnesium bromide (prepared by a known method) was investigated further. It was found, however, that the apparently anomalous behavior of this Grignard reagent was due to a lower degree of reactivity than normally encountered. When the reaction time was extended sufficiently, however, a positive Color Test I was obtained. The minimum time required for a specific concentration of cyclopentadienylmagnesium bromide to give a positive Color Test I is given in Table I.

Freshly prepared cyclopentadienyl derivatives of tin were from pale yellow to canary yellow in color, depending on the number of cyclopentadienyl groups in the molecule. On standing, all of these derivatives [(I), (II), (III), and (IV)] gradually darkened, finally turning rust brown. The rate at which this change occurred was dependent upon the number of cyclopentadienyl groups in the molecule and was accelerated by both light and air.

TABLE I

A Positive Color Test I for Cyclopentadienylmagnesium Bromide

Concentration[a] of Michler's Ketone	Concentration[b] of Cyclopentadienylmagnesium Bromide	Minimum Time, in Minutes, for Positive Test at: 30°C.	20°C.
1	0.84	3–4	15–18
1	0.68	3–4	15–18
1	0.48	3–4	15–18
1	0.27	3–4	16–18
1	0.10	4–5	16–18
0.5	0.075	6–8	16–19
0.5	0.05	6–9	16–20
0.25	0.025	9–10	20–22
0.1	0.01	>18	>30

[a] Concentration expressed in weight per cent solution of benzene. [b] Concentration expressed in moles per liter as indicated by titration with acid.

The nature of the products obtained from the spontaneous decomposition of (II), (III), and (IV) was not investigated. These decomposition products apparently resulted from a combination of oxidation and polymerization. Several observations made in the course of this investigation were suggestive of the fact that these derivatives are rather sensitive to oxidation. For example: First, on several occasions (IV) caught fire spontaneously. Second, both (III) and (IV) reacted violently with concentrated nitric acid (incidental to analysis), and the reaction was accompanied by the evolution of both heat and light. Third, the per cent of tin found on the attempted analysis of (IV) was consistently below the theoretical value, and it became progressively lower as the sample aged.

Ketone derivatives of ferrocene have been obtained through the Friedel-Crafts reaction,[4] carboxylic acid derivatives have been obtained through metalation with *n*-butyllithium followed by carbonation,[18] and substitution products have been obtained through reactions with diazonium salts.[5] In contrast, triphenyl-1-cyclopentadienyltin (I) is readily hydrolyzed by aqueous alcohol at room temperature, giving triphenyltin hydroxide; it is cleaved by bromine giving triphenyltin bromide; and it undergoes cleavage and redistribution reactions[19,20] in the presence of *n*-butyllithium, giving tetraphenyltin as the principal product.

The relative ease with which (I) was cleaved by water, as well as the pyrophoric nature of (IV) indicated that these derivatives resemble more closely the saltlike alkali metal derivatives of cyclo-

(13) Mack and Parker, U. S. Patent 2,604,483 [*C. A.*, **47**, 4358 (1953)].

(14) There has just appeared a note on the preparation of dicyclopentadienyltin by reaction of tin(II) chloride with cyclopentadienyllithium in dimethylformamide: Fischer and Grubert, *Z. Naturforschung*, 11B, 423 (1956).

(15) Grignard and Courtot, *Compt. rend.*, **158**, 1736 (1914).

(16) Courtot, *Ann. chim.*, **4**, 71 (1915).

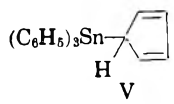
(17) Gilman and Schulze, *J. Am. Chem. Soc.*, **47**, 2002 (1925).

(18) Benkeser, *J. Am. Chem. Soc.*, **76**, 4025 (1954).

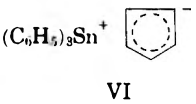
(19) Gilman, Moore, and Jones, *J. Am. Chem. Soc.*, **63**, 2482 (1941).

(20) Gilman and Arntzen, *J. Org. Chem.*, **15**, 994 (1950).

pentadiene[21] than they resemble ferrocene and its analogs. The resonance stabilization gained in the cyclopentadienyl anion of structure (VI) over the conjugated bonds of structure (V) is probably a contributing factor in the relative ease with which triphenyl-1-cyclopentadienyltin (I) undergoes hydrolytic cleavage. In any event, the relative ease



V



VI

with which these derivatives underwent hydrolytic cleavage made it desirable to purify the organotin compounds (I), (II), (III), and (IV) without first hydrolyzing the reaction mixture. This was accomplished by first concentrating the reaction mixture to a paste, then digesting this paste with a mixture of benzene and petroleum ether. The organotin compounds were soluble in this mixture, while the magnesium salts and cyclopentadienylmagnesium bromide were insoluble and could be removed by filtration.

At the time of this investigation, the preparation of triphenyl-1-indenyltin (VII) had not been reported. Subsequently, it has been prepared through the reaction of indenyllithium with triphenyltin chloride.[22] In this investigation, indenylmagnesium bromide was prepared by a previously described procedure[16,23] and treated with the appropriate organotin chloride to obtain triphenyl-1-indenyltin (VII) and diphenyldi-1-indenyltin (VIII). Under conditions analogous to those used for the hydrolysis of (I), triphenyl-1-indenyltin (VII) and diphenyldi-1-indenyltin (VIII) were not hydrolyzed.

Trimethyl-1-cyclopentadienylsilane and dimethyldi-1-cyclopentadienylsilane have been prepared by Frisch.[24] Molecular weight measurements made by this investigator[24] indicated that these derivatives were monomeric. Furthermore, the reaction of trimethyl-1-cyclopentadienylsilane and dimethyldi-1-cyclopentadienylsilane with maleic anhydride, to give the expected Diels-Alder adduct, indicated that the cyclopentadienyl ring still possessed conjugated double bonds, capable of undergoing a Diels-Alder reaction.

In the course of an earlier investigation in this laboratory[25] concerned with the synthesis of organotin compounds as potential chemotherapeutic agents, the reaction of triphenyl-2-furyltin with maleic anhydride was attempted as a possible method for introducing water-solubilizing groups into the organotin compounds. The reaction did not proceed as expected, and its failure was attributed to a reduced reactivity associated with the triphenyltin linkage.

The properties of triphenyl-1-cyclopentadienyltin (I) discussed above, suggested that this derivative might be similar to trimethyl-1-cyclopentadienylsilane, and thus, might undergo a Diels-Alder reaction. This possibility was investigated. Unlike triphenyl-2-furyltin, triphenyl-1-cyclopentadienyltin (I) reacted readily with maleic anhydride to give a good yield of 7-(triphenylstannyl)bicyclo[2.2.1]-hept-5-ene-2,3-dicarboxylic anhydride[26] (IX). Infrared analysis[27] of this derivative (IX) showed the presence of the anhydride linkage. In fact, the spectrum of this derivative was very similar to the spectra of both succinic anhydride and maleic anhydride. The spectrum of (IX) differed primarily from the spectrum of succinic anhydride in the presence of bands characteristic of a monosubstituted benzene.

An extension of this investigation, to determine the scope and the limitations of this reaction, indicated that (I) underwent Diels-Alder reactions with diethyl maleate and with diethyl acetylenedicarboxylate as well. The products isolated were 7-(triphenylstannyl)bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid diethyl ester (X) and 7-(triphenylstannyl)bicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylic acid diethyl ester (XI), respectively.

Since a Diels-Alder adduct was obtained from the reaction of triphenyl-1-cyclopentadienyltin with maleic anhydride, diethyl maleate, and diethyl acetylenedicarboxylate, the reaction of triphenyl-2-furyltin was reinvestigated. Under conditions identical with those described above for the reaction of triphenyl-1-cyclopentadienyltin with maleic anhydride, triphenyl-2-furyltin did not give an addition product. This organotin compound was recovered in 94% yield. A second attempted reaction between triphenyl-2-furyltin and maleic anhydride gave essentially the same results.

EXPERIMENTAL

All operations involving the use of Grignard reagents were run in an oxygen-free nitrogen atmosphere. All melting points are uncorrected. The tin analyses were performed according to a recent procedure.[28]

Starting materials. The tetraphenyltin was obtained from the Hooker Electrochemical Co. This was converted to triphenyltin chloride,[29] diphenyltin dichloride,[30] and phenyltin trichloride[30] by published procedures.

Cyclopentadienylmagnesium bromide. Cyclopentadienylmagnesium bromide was prepared in yields of 75–85% (as indicated by titration with hydrochloric acid), through the

(21) Thiele, *Ber.*, **34**, 68 (1901).

(22) Zimmer and Sparmann, *Naturwissenschaften*, **40**, 220 (1953); *Ber.*, **87**, 645 (1954).

(23) Grignard, Bellet, and Courtot, *Ann. chim.*, **4**, 56 (1915).

(24) Frisch, *J. Am. Chem. Soc.*, **75**, 6050 (1953).

(25) Gilman and Goreau, *J. Org. Chem.*, **17**, 1470 (1952).

(26) The nomenclature used was recommended by *Chemical Abstracts*.

(27) The authors are grateful to Dr. V. A. Fassel and Messrs. R. McCord and R. Kross of the Atomic Institute, for the infrared analyses.

(28) Gilman and Rosenberg, *J. Am. Chem. Soc.*, **75**, 3592 (1953).

(29) Gilman and Rosenberg, *J. Am. Chem. Soc.*, **74**, 5580 (1952).

(30) Gilman and Gist, *J. Org. Chem.*, in press.

reaction of ethylmagnesium bromide with cyclopentadiene according to a published procedure.[15,16]

Cyclopentadienylmagnesium bromide with Michler's ketone. A stock solution was prepared containing 1 g. of N,N,N',N'-tetramethyldiaminobenzophenone per 100 ml. of anhydrous benzene, and an aliquot of this solution was diluted with the required amount of benzene when lower concentrations of this ketone were desired.

A stoppered vial containing 1 ml. of an 0.84*M* benzene-ether solution[31] of cyclopentadienylmagnesium bromide and 1 ml. of a 1% solution of Michler's ketone was placed in a water bath at 30° for 1 min. The reaction mixture was then hydrolyzed, and treated dropwise with a 0.2% solution of iodine in glacial acid until the color of iodine did not fade. No trace of the expected green color was observed. Similarly, a negative test was obtained when the reaction mixture was hydrolyzed after 2 min. at 30°; a faint positive test was obtained after 3 min.; and a distinctly positive test after 4 min. When the reaction was carried out at 20° the time required for a positive test was considerably longer.

Lower concentrations of this Grignard reagent were obtained by diluting an aliquot with anhydrous ether. The minimum time required for a specific concentration of cyclopentadienylmagnesium bromide to give a positive Color Test I (characteristic green color) at both 20° and 30° was given in Table I.

Triphenyl-1-cyclopentadienyltin (I). A solution of 20 g. (0.05 mole) of triphenyltin chloride in 200 ml. of ether was added rapidly to a solution containing 0.1 mole of cyclopentadienylmagnesium bromide in 105 ml. of benzene-ether.[31] After heating the reaction mixture at the reflux temperature for a 4-hr. period, it was concentrated to a paste. This paste was digested twice with 200-ml. portions of a (1:1) mixture of benzene-petroleum ether (b.p. 57–70°) and filtered hot. After concentrating and cooling the filtrate, there was obtained 17.4 g. (84%) of triphenyl-1-cyclopentadienyltin which melted between 124 and 129°. After two recrystallizations from petroleum ether (b.p. 57–70°), 14.8 g. (71.5%) of pure product was obtained, melting at 130–131°.

Anal. Calcd. for $C_{23}H_{20}Sn$: Sn, 28.60. Found: Sn, 28.54, 28.70.

Diphenyldi-1-cyclopentadienyltin (II). To 115 ml. of an ether-benzene solution[31] containing 0.1 mole of cyclopentadienylmagnesium bromide was added 8.7 g. (0.025 mole) of diphenyltin dichloride dissolved in 100 ml. of ether. The reaction mixture was heated at the reflux temperature for a period of 48 hr., then concentrated to a paste. The paste was digested twice with 200-ml. portions of a (1:1) mixture of benzene-petroleum ether (b.p. 57-70°) and filtered hot. After the solvents had been removed at 50° under reduced pressure, the residue was dissolved in a minimum of hot petroleum ether (b.p. 57–70°) and cooled in a bath of dry ice. The crude product obtained (10.7 g. melting between 97 and 101°) was recrystallized first from petroleum ether (b.p. 57–70°), then from carbon tetrachloride, to give 7.1 g. (70%) of pure diphenyldi-1-cyclopentadienyltin, melting at 105–106°.

Anal. Calcd. for $C_{22}H_{20}Sn$: Sn, 29.45. Found: Sn, 29.50, 29.54.

Phenyltri-1-cyclopentadienyltin (III). To 285 ml. of an ether-benzene solution[31] containing 0.3 mole of cyclopentadienylmagnesium bromide was added 15.1 g. (0.05 mole) of phenyltin trichloride dissolved in 30 ml. of benzene. After 100 ml. of ether had been added, the reaction mixture was heated at the reflux temperature for 16 hr., then concentrated to a paste. This residue was digested three times with 200-ml. portions of petroleum ether (b.p. 57–70°) and the insoluble materials were removed by filtration. The filtrate was concentrated to 100 ml., and then cooled in a bath of dry ice–acetone. The product was removed by filtration, and dried in a vacuum desiccator to obtain 18.0 g. (59%) of crude phenyltri-1-cyclopentadienyltin melting over the range 43–60°. The product (III) was dissolved in a minimum of boiling petroleum ether (b.p. 57–70°), the amorphous rust brown solid was removed by filtration, and the filtrate was cooled in a bath of acetone and dry ice to obtain 12.13 g. (40%) of pure product melting at 64–65°.

Anal. Calcd. for $C_{21}H_{20}Sn$: Sn, 30.36. Found: Sn, 30.38, 30.49.

On exposure to air, a sample of (III) turned rust brown within 4 hr., and the resulting compound decomposed without melting over the range of 200–220°. This rust brown solid was not investigated.

Tetra-1-cyclopentadienyltin (IV). To 415 ml. of an ether-benzene solution[31] containing 0.4 mole of cyclopentadienylmagnesium bromide was added 13.05 g. (0.05 mole) of anhydrous tin(IV) chloride diluted with 40 ml. of benzene. The mixture was heated at the reflux temperature for a period of 24 hr., and then concentrated to a paste. The resulting paste was digested three times with 200-ml. portions of petroleum ether (b.p. 57–70°) and the resulting solutions were filtered hot. The combined filtrate was concentrated under reduced pressure to a volume of 100 ml., and then cooled in a dry ice–acetone bath to obtain 12.5 g. of crude material melting between 71 and 75°. (After drying this product in a vacuum desiccator over paraffin for 3 hr., the weight and the melting point were determined.) The crude product was dissolved in a minimum of hot petroleum ether (b.p. 57–70°), and filtered hot to remove 2.42 g. of amorphous brown solid. The filtrate was cooled in a dry ice–acetone bath to obtain 8.70 g. (41.5%) of relatively pure material melting at 71–73°.

The infrared spectrum of freshly prepared (IV), when determined in carbon disulfide, as well as in bromoform, did not differ essentially from the spectrum of either (I), (II), or (III), except for an increase in the intensity of the bands characteristic of conjugated double bonds, and a complete absence of the bands characteristic of monosubstituted benzene. When this compound was subjected to analysis for tin, however, the results were less informative. After drying the product for 24 hr. and for 72 hr. in a vacuum desiccator, this derivative gave results that were 2.67% and 3.95% below the theoretical value, respectively.

Anal. Calcd. for $C_{20}H_{20}Sn$: Sn, 31.32. Found (24 hr.): Sn, 28.60, 28.71. Found (72 hr.): Sn, 27.23, 27.52.

Indenylmagnesium bromide. Indenylmagnesium bromide was prepared by a published procedure.[16,23] The resulting product was used as a fine suspension. The heterogeneous nature of this organometallic compound made it undesirable to transfer this reagent or to determine its yield. An excess of this intermediate was, therefore, used in all subsequent reactions.

Triphenyl-1-indenyltin (VII). To a suspension of 0.2 mole of indenylmagnesium bromide in 600 ml. of ether was added 38.5 g. (0.10 mole) of triphenyltin chloride in 300 ml. of ether. The mixture was heated at the reflux temperature for a period of 48 hr., cooled to room temperature, and then poured slowly into an aqueous ammonium chloride solution. The organic layer was separated, dried over calcium sulfate for 24 hr., and then concentrated. The unreacted indene was removed under reduced pressure, and the residue was crystallized from chloroform-petroleum ether (b.p. 57–70°) to obtain 23.9 g. (54%) of crude triphenyl-1-indenyltin, melting over the range of 111–123°. After two recrystallizations from the same solvent pair 21.0 g. (45.5%) of pure product (VII) was obtained, melting at 129–130°.

Anal. Calcd. for $C_{27}H_{22}Sn$: Sn, 25.52. Found: Sn, 25.50, 25.55.

Diphenyldi-1-indenyltin (VIII). To a suspension of 0.4 mole of indenylmagnesium bromide in one liter of ether was added 34.4 g. (0.10 mole) of diphenyltin dichloride in 100

(31) This benzene-ether solution had a boiling point of 60°. A solution with this boiling point is obtained when cyclopentadienylmagnesium bromide is prepared according to the procedure of Courtot.[16]

ml. of ether. The mixture was heated at the reflux temperature for a period of 24 hr., concentrated to half-volume, and heated at the reflux temperature for an additional 24 hr. The reaction mixture was hydrolyzed with aqueous ammonium chloride, the organic layer was separated and dried for 24 hr. over calcium sulfate, and the solvents were removed. The indene was removed under reduced pressure. The residue was crystallized from a (1:1) mixture of chloroform-petroleum ether (b.p. 57–70°) to obtain 21.2 g. (42%) of crude (VIII), melting between 81 and 103°. After two recrystallizations from the same solvent pair 14.8 g. (29.9%) of pure diphenyldi-1-indenyltin (VIII) was obtained, melting at 108–110°. Subsequent recrystallization of this product did not improve the melting point.

Anal. Calcd. for $C_{30}H_{24}Sn$: Sn, 23.59. Found: Sn, 23.62, 23.67.

REACTIONS OF TRIPHENYL-1-CYCLOPENTADIENYLTIN (I)

With water. In one experiment, a solution of 4.15 g. (0.01 mole) of triphenyl-1-cyclopentadienyltin in 100 ml. of 95% ethanol was heated at the reflux temperature for 15 min., and then concentrated to near dryness. The resulting oil was dehydrated by azeotropic distillation using benzene, and crystallized from petroleum ether (b.p. 57–70°) to obtain 3.30 g. (92%) of bis(triphenyltin)oxide, melting at 123–124°. A mixture melting point with an authentic specimen was not depressed.

In another experiment, 4.15 g. (0.01 mole) of triphenyl-1-cyclopentadienyltin was dissolved in 100 ml. of 95% ethanol at room temperature, the flask was stoppered and allowed to stand for 24 hr., and then poured into ice water. The product obtained weighed 3.72 g. and melted over the range of 112–117°. This compound was dehydrated by azeotropic distillation using benzene, and then recrystallized from petroleum ether (b.p. 57–70°) to obtain 2.91 g. (81%) of bis(triphenyltin)oxide, melting sharply at 124°. A mixture melting point with an authentic specimen was not depressed.

With n-butyllithium. A solution of 0.03 mole of *n*-butyllithium in 35 ml. of ether was added dropwise at room temperature to a solution of 12.45 g. (0.03 mole) of triphenyl-1-cyclopentadienyltin dissolved in 200 ml. of a (1:1) mixture of benzene-ether. The mixture became turbid almost immediately, and later developed into a heavy gelatinous mass. One-half hour after the addition had been completed, the mixture was poured into a slurry of ether and dry ice, and the carbonated product was allowed to come to room temperature. The mixture was hydrolyzed with water, filtered, and the two layers were separated. The 7.1 g. of solid removed by filtration was subsequently recrystallized from benzene to obtain 5.2 g. (46.5%) of tetraphenyltin melting at 224–225°. A mixture melting point with an authentic specimen showed no depression.

An oil weighing 3.1 g. was obtained by concentrating the ether layer. This oil was not resolved into any pure products.

After acidification of the water layer, and extracting the organic material, 1.7 g. of an acidic oil was removed, which gave a negative qualitative test for tin.[25] This material was not investigated further.

The reaction of triphenyl-1-cyclopentadienyltin with *n*-butyllithium was also investigated at the temperature of a dry ice–acetone bath, using a mixture of ether and toluene as the solvent of the reaction. Under conditions otherwise identical to those described above, a 33% yield of tetraphenyltin was obtained melting at 222–224°.

With bromine. To 12.45 g. (0.03 mole) of triphenyl-1-cyclopentadienyltin in 250 ml. of carbon tetrachloride was added 4.8 g. (0.03 mole) of bromine dissolved in 100 ml. of carbon tetrachloride. The dropwise addition was carried out at room temperature. The color of the bromine was discharged almost instantaneously. After the addition had been completed, the solvent was removed by distillation, and the product was crystallized from petroleum ether (b.p. 57–70°) to obtain 7.8 g. (60.5%) of crude triphenyltin bromide melting over the range of 99–106°. After recrystallization from the same solvent, 6.7 g. (52%) of triphenyltin bromide was obtained melting at 120–121°. A mixture melting point with an authentic specimen showed no depression.

With maleic anhydride. To a solution of 12.45 g. (0.03 mole) of triphenyl-1-cyclopentadienyltin in 30 ml. of benzene was added a suspension of 2.94 g. (0.03 mole) of maleic anhydride in 20 ml. of benzene. The mixture became warm spontaneously. After the initial reaction had subsided, the mixture was heated at the reflux temperature for 1 hr., then the benzene was removed by distillation. The crude product was digested with 50 ml. of petroleum ether (b.p. 57–70°) to remove any unreacted starting material, cooled, and filtered. The residue was recrystallized from carbon tetrachloride to obtain 11.0 g. of crude 7-(triphenylstannyl)-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride[26] (IX) melting between 138 and 150°. After two recrystallizations from carbon tetrachloride 9.1 g. (59%) of pure product was obtained, melting at 144–145°. A duplicate reaction gave essentially the same results. This product was too insoluble to determine the neutral equivalent.

Infrared analysis of this derivative showed the acid anhydride absorption bands characteristic in the spectra of maleic anhydride and succinic anhydride.

Anal. Calcd. for $C_{27}H_{22}O_3Sn$: Sn, 23.13. Found: Sn, 22.83, 23.03.

With diethyl maleate. To a solution of 12.45 g. (0.03 mole) of triphenyl-1-cyclopentadienyltin dissolved in 50 ml. of benzene was added 5.67 g. (0.033 mole) of diethyl maleate, and the mixture was heated at the reflux temperature for a 4-hr. period. The solvent was removed under reduced pressure, and the resulting oil (20 g.) was dissolved in 100 ml. of not methanol, filtered, concentrated, and cooled to obtain 10.4 g. (59%) of crude product, melting between 101–106°. Two subsequent recrystallizations from 75% ethanol gave 8.8 g. (49.9%) of relatively pure 7-(triphenylstannyl)-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid diethyl ester[26] (X), melting at 107–109.5°. From this product an analytical sample was obtained by an additional recrystallization from diethyl ether using a dry ice–acetone bath. The analytical sample melted at 109.5–111°.

Anal. Calcd. for $C_{31}H_{32}O_4Sn$: Sn, 20.21. Found: Sn, 20.25, 20.29.

With diethyl acetylenedicarboxylate. A solution of 12.45 g. (0.03 mole) of triphenyl-1-cyclopentadienyltin dissolved in 300 ml. of ether was treated with 5.10 g. (0.03 mole) of the diethyl acetylenedicarboxylate. The mixture was heated at the reflux temperature for a period of six hr., concentrated to 150 ml. and cooled in a dry ice–acetone bath. The crystallized product was removed by filtration; the mother liquor was concentrated to 50 ml. and returned to the bath. The first crop of crystals weighed 4.3 g. and melted over the range of 100–104°, while the second crop weighed 5.3 g. and melted over the range of 97–102°. The combined crude product (7.6 g. or 44.5%) of 7-(triphenylstannyl)bicyclo-[2.2.1]hepta-2,5-diene-2,3-dicarboxylic acid diethyl ester[26] was twice recrystallized from diethyl ether to obtain 6.9 g. of pure product melting at 107–108°.

A duplicate reaction gave essentially the same results.

Anal. Calcd. for $C_{31}H_{30}O_4Sn$: C, 63.60; H, 5.18; Sn, 20.28. Found: C, 63.22, 63.15; H, 4.92, 5.10; Sn, 20.13, 20.10.

Triphenyl-2-furyltin with maleic anhydride. To a solution of 4.17 g. (0.01 mole) of triphenyl-2-furyltin in 10 ml. of benzene was added a suspension of 0.98 g. (0.01 mole) of maleic anhydride in 10 ml. of benzene. The mixture was heated at the reflux temperature for a period of one hr., the benzene was removed by distillation, and the crude product was recrystallized from carbon tetrachloride to obtain 3.94 g. (94% recovery) of triphenyl-2-furyltin, melting at 160–

161°. A mixture melting point with an authentic specimen was not depressed.

For a duplicate reaction 3.73 g. (88%) of triphenyl-2-furyltin was recovered, melting at 159–160°.

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AMES, IOWA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF WESTERN ONTARIO]

Organometallic Reactions of ω-Fluoroalkyl Halides. II.[1,2] Reactions of ω-Fluoroalkylmagnesium Chlorides

W. C. HOWELL, W. J. COTT, AND F. L. M. PATTISON

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The study of Grignard reagents formed from ω-fluoroalkyl halides has been extended to include a variety of typical reactions through the use of such reagents as acid chlorides, acid anhydrides, ethylene oxide, benzonitrile, and triethyl orthoformate. This has led to new methods for preparing ω-fluorocarboxylic esters, ω-fluoroalkyl ketones, ω-fluoroalcohols and ω-fluoroaldehydes, all of which are of pharmacological interest.

In the preceding paper of this series[2] a general method was outlined for the preparation of Grignard reagents from various ω-fluoroalkyl halides. From this study, the longer chain ω-fluoroalkyl chlorides (C_6–C_{10}) emerged as potentially valuable intermediates in the synthesis of new ω-fluoroalkylated derivatives. At that time, however, it was established only that these Grignard reagents reacted with carbon dioxide. To determine the general usefulness of the method, other reactions have been examined both for the diversity of reaction type, and for possible pharmacological interest of the products. The reactants selected were: (*a*) *Ethyl chloroformate:* reaction of a carbonyl halide; formation of ω-fluorocarboxylic esters.[3,4] (*b*) *Acid chlorides:* reaction of a carbonyl halide; formation of ω-fluoroalkyl ketones.[5] (*c*) *Carboxylic anhydrides:* addition to a carbonyl group; formation of ω-fluoroalkyl ketones.[5] (*d*) *Ethylene oxide:* cleavage of an epoxide; formation of ω-fluoroalcohols.[6] (*e*) *Benzonitrile:* addition to an unsaturated C—N system; formation of ω-fluoroalkyl phenyl ketones.[5] (*f*) *Triethyl orthoformate:* cleavage of an ether-acetal; formation of ω-fluoroaldehydes.[7]

First to be examined were the reactions of ω-fluoroalkylmagnesium chlorides with ethyl chloroformate[8–10] giving rise to ω-fluorocarboxylic esters. A large excess of chloroformate was used and the reaction was completed by heating for a short time under reflux; by this means, tertiary alcohol formation was minimized, but ketones were occasionally isolated, formed by reaction of excess Grignard reagent with the main product. A representative example is described in the Experimental section, and results are summarized in Table I. Similar conditions were found to be satisfactory for the use of acid chlorides[11] in the preparation of ω-fluoroalkyl ketones, although tertiary alcohol formation appeared to occur to a greater extent than in the reactions with ethyl chloroformate. The lower ω-fluorocarboxylic acid chlorides failed to react under the conditions employed; thus fluoroacetyl chloride, 3-fluoropropionyl chloride, 4-fluorobutyryl chloride and 5-fluorovaleryl chloride gave none of the desired ketones. The successful reactions are shown in Table I.

The use of carboxylic anhydrides[12–16] for the preparation of ketones was next investigated. A series of ω-fluoroalkyl methyl ketones (Table I)

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(1) (*a*) Issued as DRB Report No. SW-29. (*b*) To avoid ambiguity, fluorine is not generally referred to as halogen in this communication.

(2) Part I, F. L. M. Pattison and W. C. Howell, *J. Org. Chem.*, **21**, 879 (1956).

(3) F. J. Buckle, F. L. M. Pattison, and B. C. Saunders, *J. Chem. Soc.*, 1471 (1949).

(4) F. L. M. Pattison, S. B. D. Hunt, and J. B. Stothers, *J. Org. Chem.*, **21**, 883 (1956).

(5) R. R. Fraser, J. E. Millington, and F. L. M. Pattison, *J. Am. Chem. Soc.*, in press.

(6) F. L. M. Pattison, W. C. Howell, A. J. McNamara, J. C. Schneider, and J. F. Walker, *J. Org. Chem.*, **21**, 739 (1956).

(7) J. F. K. Wilshire and F. L. M. Pattison, *J. Am. Chem. Soc.*, **78**, 4996 (1956).

(8) J. Houben, *Ber.*, **36**, 3087 (1903).

(9) R. Gaertner, *J. Am. Chem. Soc.*, **73**, 3934 (1951).

(10) A. I. Krutman, *J. Gen. Chem.* (*U.S.S.R.*), **22**, 1385 (1952) (Engl. translation).

(11) W. C. Percival, R. B. Wagner, and N. C. Cook, *J. Am. Chem. Soc.*, **75**, 3731 (1953).

(12) Tissier and Grignard, *Compt. rend.*, **132**, 683 (1901).

(13) H. Fournier, *Bull. soc. chim. France*, [3], **31**, 483 (1904); [3], **35**, 19 (1906); [4], **7**, 836 (1910).

(14) M. S. Newman and W. T. Booth, *J. Am. Chem. Soc.*, **67**, 154 (1945).

(15) M. S. Newman and T. J. O'Leary, *J. Am. Chem. Soc.*, **68**, 258 (1946).

(16) M. S. Newman and A. S. Smith, *J. Org. Chem.*, **13**, 592 (1948).

TABLE I

GRIGNARD REACTIONS OF ω-FLUOROALKYL CHLORIDES

ω-Fluoroalkyl Chloride	Reagent	Product	Yield, %	Disubstitution Product	Yield, %
$F(CH_2)_6Cl$	ClCOOEt	Ethyl 7-fluoroheptanoate $F(CH_2)_6COOEt$	48	Diethyl suberate[a] $EtOOC(CH_2)_6COOEt$	6
$F(CH_2)_7Cl$	ClCOOEt	Ethyl 8-fluorooctanoate $F(CH_2)_7COOEt$	49	Diethyl azelate[a] $EtOOC(CH_2)_7COOEt$	8
$F(CH_2)_8Cl$	ClCOOEt	Ethyl 9-fluorononanoate $F(CH_2)_8COOEt$	54.5	Diethyl sebacate[a] $EtOOC(CH_2)_8COOEt$	10
$F(CH_2)_9Cl$	ClCOOEt	Ethyl 10-fluorodecanoate[b] $F(CH_2)_9COOEt$	61	Diethyl undecanedioate[a] $EtOOC(CH_2)_9COOEt$	6
$F(CH_2)_{10}Cl$	ClCOOEt	Ethyl 11-fluoroundecanoate[c] $F(CH_2)_{10}COOEt$	54	Diethyl dodecanedioate[a] $EtOOC(CH_2)_{10}COOEt$	4
$F(CH_2)_6Cl$	CH_3COCl	8-Fluoro-2-octanone $F(CH_2)_6COCH_3$	47		
$F(CH_2)_6Cl$	$CH_3(CH_2)_4COCl$	12-Fluoro-6-dodecanone $F(CH_2)_6CO(CH_2)_4CH_3$	49		
$F(CH_2)_6Cl$	$F(CH_2)_5COCl$	1,12-Difluoro-6-dodecanone[d] $F(CH_2)_6CO(CH_2)_5F$	51		
$F(CH_2)_6Cl$	$F(CH_2)_6COCl$	1,13-Difluoro-7-tridecanone[e] $F(CH_2)_6CO(CH_2)_6F$	55		
$F(CH_2)_6Cl$	$(CH_3CO)_2O$	8-Fluoro-2-octanone $F(CH_2)_6COCH_3$	59	2,9-Decanedione[f] $CH_3CO(CH_2)_6COCH_3$	17
$F(CH_2)_7Cl$	$(CH_3CO)_2O$	9-Fluoro-2-nonanone $F(CH_2)_7COCH_3$	64	2,10-Undecanedione[f] $CH_3CO(CH_2)_7COCH_3$	16
$F(CH_2)_8Cl$	$(CH_3CO)_2O$	10-Fluoro-2-decanone $F(CH_2)_8COCH_3$	68	2,11-Dodecanedione[f] $CH_3CO(CH_2)_8COCH_3$	19
$F(CH_2)_9Cl$	$(CH_3CO)_2O$	11-Fluoro-2-undecanone $F(CH_2)_9COCH_3$	65	2,12-Tridecanedione[f] $CH_3CO(CH_2)_9COCH_3$	21
$F(CH_2)_{10}Cl$	$(CH_3CO)_2O$	12-Fluoro-2-dodecanone $F(CH_2)_{10}COCH_3$	64	2,13-Tetradecanedione[f] $CH_3CO(CH_2)_{10}COCH_3$	22
$F(CH_2)_6Cl$	$[F(CH_2)_5CO]_2O$	1,12-Difluoro-6-dodecanone[d] $F(CH_2)_6CO(CH_2)_5F$	47		
$F(CH_2)_6Cl$	$(CH_2)_2O$	8-Fluorooctanol $F(CH_2)_8OH$	46	1,10-Decanediol $HO(CH_2)_{10}OH$	4
$F(CH_2)_8Cl$	C_6H_5CN	8-Fluorooctyl phenyl ketone $F(CH_2)_8COC_6H_5$	70	1,8-Dibenzoyloctane[g] $C_6H_5CO(CH_2)_8COC_6H_5$	10
$F(CH_2)_8Cl$	$HC(OC_2H_5)_3$	9-Fluorononanal $F(CH_2)_8CHO$	37[h]	Sebacaldehyde $OHC(CH_2)_8CHO$	43[i]

[a] Identified by hydrolysis to the corresponding acid, followed by mixed melting point determination with authentic sample. [b] Also isolated was 1,19-difluoro-10-nonadecanone, $F(CH_2)_9CO(CH_2)_9F$ (11% yield), formed by reaction of excess Grignard reagent with the main product. [c] Also isolated was 1,21-difluoro-11-heneicosanone, $F(CH_2)_{10}CO(CH_2)_{10}F$ (4% yield), formed by reaction of excess Grignard reagent with the main product. [d] Also isolated was 5-fluoroamyl-*bis*-6-fluorohexylcarbinol, $F(CH_2)_5C(OH)[(CH_2)_6F]_2$ (10% yield), formed by reaction of excess Grignard reagent with the main product. [e] Also isolated was *tris*-6-fluorohexylcarbinol, $[F(CH_2)_6]_3COH$ (11% yield), formed by reaction of excess Grignard reagent with the main product. [f] Identified by melting point and formation of 2,4-dinitrophenylhydrazone. [g] Identified by melting point and formation of dioxime. [h] Total yield of free aldehyde and corresponding diethyl acetal; yield of pure, free aldehyde was 25%. [i] High yield of disubstitution product was possibly due to prolonged refluxing with excess magnesium.

was prepared by the interaction of the appropriate ω-fluoroalkylmagnesium chloride with acetic anhydride under essentially the same conditions as those recommended by Newman and Smith.[16] Of the ω-fluorocarboxylic anhydrides examined, fluoroacetic anhydride and 3-fluoropropionic anhydride failed to react under the conditions employed, but 6-fluorohexanoic anhydride formed the expected 1,12-difluoro-6-dodecanone in 47% yield.

Several reactions were studied in less detail. The use of ethylene oxide for forming primary alcohols[17] was illustrated by the conversion of 6-fluorohexyl chloride to 8-fluorooctanol. 8-Fluorooctyl phenyl ketone was prepared from 8-fluorooctylmagnesium chloride by treatment with benzonitrile; this procedure afforded a general route to the new series of ω-fluoroalkyl phenyl ketones, the pharmacological properties of which could be compared with the corresponding ω-fluoroalkyl methyl ketones.[5] Finally, the Bodroux-Tschitschibabin synthesis[18,19] was examined as a means of preparing ω-fluoroaldehydes, which have been obtained only with difficulty by other conventional methods.[7] Treatment of 8-fluorooctylmagnesium chloride with triethyl orthoformate in the usual manner[20,21]

(17) R. C. Huston and C. C. Langham, *J. Org. Chem.*, 12, 90 (1947).

(18) F. Bodroux, *Compt. rend.*, 138, 92, 700 (1904).

(19) A. E. Tschitschibabin, *Ber.*, 37, 186, 850 (1904).

(20) L. I. Smith and M. Bayliss, *J. Org. Chem.*, 6, 437 (1941).

(21) L. I. Smith and J. Nichols, *J. Org. Chem.*, 6, 489 (1941).

TABLE II

PHYSICAL CONSTANTS AND ANALYTICAL DATA

Compound	Boiling Point °C.	Mm.	n_D^{25} or M.P., °C.	C, % Calcd.	C, % Found	H, % Calcd.	H, % Found	N, % Calcd.	N, % Found
$F(CH_2)_6COOEt$	97–97.5	11	1.4111	61.34	61.32	9.72	9.52		
$F(CH_2)_7COOEt$[a]	106.5–107	9	1.4158	63.13	63.08	10.07	9.72		
$F(CH_2)_8COOEt$	120–120.5	9	1.4191	64.67	64.42	10.36	10.16		
$F(CH_2)_9COOEt$[b]	136–136.5	11	1.4228	66.02	65.62	10.62	10.32		
$F(CH_2)_{10}COOEt$[c]	145–146	9	1.4257	67.20	67.19	10.85	10.74		
$F(CH_2)_6COCH_3$	87–88	11	1.4132	65.73	65.65	10.34	10.11		
DNP[d,e]			82					17.17	17.12
$F(CH_2)_7COCH_3$	98–98.5	9	1.4180	67.45	67.73	10.70	10.92		
DNP[e]			65					16.47	16.65
$F(CH_2)_8COCH_3$	113–113.5	9	1.4213	68.92	68.60	10.99	10.98		
DNP[e]			83.5					15.81	15.57
$F(CH_2)_9COCH_3$	126–126.5	9.5	1.4258	70.16	69.84	11.24	11.00		
DNP[e]			70					15.21	15.48
$F(CH_2)_{10}COCH_3$	138–138.5	9.5	1.4288	71.24	71.07	11.46	11.44		
DNP[e]			87.5					14.65	14.44
$F(CH_2)_6CO(CH_2)_4CH_3$	138.5–139	13	1.4278	71.24	71.38	11.46	11.45		
DNP[e]			47.5					14.65	14.43
$F(CH_2)_6CO(CH_2)_5F$	136–136.5	4	1.4254	65.42	65.44	10.07	10.15		
DNP[e]			41					14.00	14.24
$F(CH_2)_6CO(CH_2)_5F$	99–99.5	0.18	1.4292	66.62	66.58	10.33	10.23		
			23						
DNP[e]			21					13.52	13.45
$F(CH_2)_9CO(CH_2)_9F$[f]			59	71.64	71.60	11.40	11.53	318.5[g]	313[g]
$F(CH_2)_{10}CO(CH_2)_{10}F$[f]			64.5	72.78	73.04	11.63	11.56	346.5[g]	337[g]
$F(CH_2)_8CHO$	99–100	9	1.4220	67.50	67.54	10.70	10.82		
DNP[e]			101.5					16.46	16.36
$F(CH_2)_8COC_6H_5$[h]	134–137	0.7	1.4983	76.23	76.30	8.96	8.80		
DNP[i]			129.5					13.46	13.82
$F(CH_2)_9OH$[j]	106–108	9	1.4248						
$F(CH_2)_6C(OH)[(CH_2)_6F]_2$[f]			72	66.68	66.69	10.80	10.78		
$[F(CH_2)_6]_3COH$[f]			74	67.46	67.52	10.95	10.77		

[a] Buckle *et al.*[3] report b.p. 191°. [b] Buckle *et al.*[3] report b.p. 135–138° (10 mm.). [c] Buckle *et al.*[3] report b.p. 140–141° (11 mm.). [d] DNP = 2,4-dinitrophenylhydrazone. [e] Recrystallized from methanol. [f] Recrystallized from petroleum ether (30–60°). [g] Molecular weight (Rast). [h] M.p. *ca.* 20°. [i] Recrystallized from ethanol. [j] Pattison *et al.*[6] report b.p. 111.5–112° (12 mm.) and n_D^{25} 1.4248.

gave a low yield of 9-fluorononanal. Hydrolysis of the acetal formed in the initial reaction proved difficult, with the result that a pure sample of aldehyde was obtained only after several distillations. Results of the above reactions are shown in Table I.

From this work, it is evident that Grignard reagents formed from ω-fluoroalkyl chlorides undergo the normal reactions in satisfactory yield. As observed in the carbonation reaction previously described,[2] moderate amounts of material formed by replacement of both fluorine and chlorine were obtained from the distillation residues (Table I); a few of the residues were not examined, since disubstitution in the case of 6-fluorohexyl chloride had already been fully substantiated in this and earlier work. It is hoped that some theoretical aspects of this problem will be discussed in another communication. In conformity with previous work,[22] the new compounds have been submitted for pharmacological examination, the results of which will be reported elsewhere.[5] Physical constants and analytical results are shown in Table II.

(22) F. L. M. Pattison, *Nature*, 172, 1139 (1953); 174, 737 (1954). See also *J. Org. Chem.*, 21, 739 (1956) and subsequent papers in the series.

EXPERIMENTAL[23]

Materials. ω-Fluoroalkyl halides were prepared in the usual manner.[24] ω-Fluorocarboxylic acid chlorides and anhydrides were prepared as described previously[25]; using the isopropenyl acetate method,[26] improved yields were obtained for fluoroacetic anhydride (79%) and for 3-fluoropropionic anhydride (75%). Commercial samples of ethyl chloroformate, acetic anhydride, benzonitrile, and triethyl orthoformate were fractionated prior to use. Ethylene oxide, Eastman Reagent, was used directly from a fresh ampoule.

Grignard reagents. In each case, the ω-fluoroalkyl chlorides were converted to the corresponding Grignard reagents in the apparatus and under the conditions described in Part

(23) (a) The microanalyses were performed by Mr. J. F. Alicino, Metuchen, N. J., and by the Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. (b) Melting points and boiling points are uncorrected, unless specified.

(24) F. L. M. Pattison and W. C. Howell, *J. Org. Chem.*, 21, 748 (1956).

(25) F. L. M. Pattison, R. R. Fraser, G. J. O'Neill, and J. F. K. Wilshire, *J. Org. Chem.*, 21, 887 (1956).

(26) H. J. Hagemeyer and D. C. Hull, *Ind. Eng. Chem.*, 41, 2920 (1949).

I of this series.[2] The subsequent reactions were usually carried out in the subsidiary apparatus.[2]

Grignard reactions. Most of the reactions were carried out only once, hence the yields reported are not necessarily the highest obtainable. The experimental conditions were uniform for each type of reaction, of which the following examples are representative.

(*a*) *Ethyl 7-fluoroheptanoate.* The Grignard reagent was prepared from 6-fluorohexyl chloride (10.0 g., 0.072 mole), ether (70 ml.) and magnesium (3.0 g., 0.124 g. atom). After filtration under nitrogen pressure, the Grignard solution was added dropwise over 1.75 hr. to a stirred solution of ethyl chloroformate (42.0 g., 0.40 mole) in 75 ml. of ether. The reaction vessel was cooled to −75° in a Dewar flask containing a slurry of powdered Dry-Ice in acetone. Stirring was continued for an additional hour and then the mixture was allowed to stand overnight in the cold. The clear yellowish solution was then stirred while warming to room temperature. During this period a fine white precipitate gradually separated. The reaction was completed by gentle refluxing for 1 hr. After cooling and addition of excess 10% sulfuric acid, the product was separated by ether extraction. The extract was washed successively with water, 10% sodium carbonate solution, and again with water. After drying over magnesium sulfate, the extract was concentrated and the residue fractionated. Excess ethyl chloroformate and unreacted 6-fluorohexyl chloride (1 g.) were recovered. Further distillation yielded 5.5 g. (48%) of ethyl 7-fluoroheptanoate. Distillation of the residue under high vacuum gave two fractions, (*a*) b.p. 56–57° (0.1 mm.), n_D^{25} 1.4212 and (*b*) b.p. 82–84° (0.1 mm.), n_D^{25} 1.4302. Hydrolysis of fraction (*b*) with alkali gave a small quantity (6%) of suberic acid, m.p. 140–141°.

(*b*) *1,13-Difluoro-7-tridecanone.* The Grignard reagent, prepared from 6-fluorohexyl chloride (10.0 g., 0.072 mole), ether (70 ml.) and magnesium (3.0 g., 0.124 g. atom), was filtered from the excess magnesium and added fairly rapidly (over about 15 min.) to a mixture of 7-fluoroheptanoyl chloride (30 g., 0.18 mole) and anhydrous, resublimed ferric chloride (0.27 g.) in ether (25 ml.); the reaction vessel was cooled by means of an acetone–dry ice bath. The mixture was stirred for 1 hr. further and then was allowed to stand overnight in the cold. The cold bath was removed and the mixture was allowed to warm to room temperature. After being stirred for 30 min., the mixture was hydrolyzed with ice water. The resultant mixture was neutralized with sodium carbonate, and extracted several times with ether. The extracts were washed with water and dried over sodium sulfate. After removal of the ether, the residue on fractionation gave 0.9 g. of unreacted 6-fluorohexyl chloride, followed by 1,13-difluoro-7-tridecanone (8.5 g., 55%).

The *2,4-dinitrophenylhydrazone* was recrystallized from methanol as orange microcrystals.

The distillation residue solidified to pale yellowish crystals. Recrystallization from petroleum ether (30–60°) gave colorless crystals of *tris-6-fluorohexylcarbinol* (1.2 g., 11%).

(*c*) *11-Fluoro-2-undecanone.* The Grignard reagent, prepared from 9-fluorononyl chloride (13.0 g., 0.072 mole), ether (75 ml.) and magnesium (3.0 g., 0.124 g. atom), was filtered from the excess magnesium and added dropwise over 1.5 hr. to a stirred solution of acetic anhydride (21.0 g., 0.21 mole) in 50 ml. of ether cooled in an acetone–dry ice bath. Stirring was continued for an additional hour. After standing overnight in the cold, the reaction mixture was allowed to warm to about 0° and then was hydrolyzed by addition of a minimum quantity (10–14 ml.) of saturated ammonium chloride solution. The product was extracted with ether, and the extracts, after successive washings with water, 5% sodium hydroxide and water, were dried over sodium sulfate or magnesium sulfate. Fractionation of the product gave 2.86 g. of unchanged 9-fluorononyl chloride, followed by 11-fluoro-2-undecanone (6.88 g., 65%).

The *2,4-dinitrophenylhydrazone* was recrystallized from methanol as long orange needles.

The distillation residue (2.49 g.) solidified to pale yellowish crystals. Recrystallization from petroleum ether (30–60°) gave colorless prisms of 2,12-tridecanedione, m.p. 71–72° (corr.). (Canonica and Bacchetti[27] report m.p. 72°.) The *bis*-2,4-dinitrophenylhydrazone, m.p. 165.5–166.5° (corr.) was recrystallized from pyridine as orange microcrystals.

(*d*) *8-Fluorooctanol.* The Grignard reagent was prepared from 6-fluorohexyl chloride (10.0 g., 0.072 mole), ether (70 ml.) and magnesium (3.0 g., 0.124 g. atom). When the reaction of the fluorochloride with the magnesium appeared to be complete (7 hr.), 50 ml. of ether were distilled into the dropping funnel around which had been fitted a cardboard jacket filled with powdered dry ice. Cold ethylene oxide (8 ml., 7 g., 0.16 mole) was quickly added to the ether. The reaction vessel was cooled in an ice-salt bath while the ether solution of ethylene oxide was added over 15 min. to the stirred Grignard solution. The ice bath was removed and the reaction mixture was stirred for 1 hr. at room temperature. After decantation of the product onto ice and cautious acidification with hydrochloric acid, the organic layer was separated and the aqueous layer extracted with additional quantities of ether. The extracts were combined, washed successively with water, 10% sodium carbonate and water, and dried over sodium sulfate. The dried extracts were concentrated and the residue was fractionated under reduced pressure. After a large forerun (*ca.* 4 g.) of ethylene chlorohydrin, b.p. 30–32° (10 mm.), unreacted 6-fluorohexyl chloride (1.15 g.) was collected at b.p. 52–60° (9 mm.), followed by 8-fluorooctanol (4.37 g., 46%). From the semisolid distillation residue was isolated a small quantity (4%) of 1,10-decanediol by crystallization from benzene, m.p. 68–70°. No depression in melting point was observed when mixed with an authentic sample.

(*e*) *8-Fluorooctyl phenyl ketone.* A solution of benzonitrile (7.4 g., 0.072 mole) in 15 ml. of ether was added rapidly with stirring at room temperature to the Grignard reagent prepared from 8-fluorooctyl chloride (12.0 g., 0.072 mole), ether (70 ml.) and magnesium (3.0 g., 0.124 g. atom). Stirring was continued and during the next 10 min. an exothermic reaction took place accompanied by the formation of a colorless precipitate. When this reaction abated, the mixture was boiled gently for 1 hr. After standing overnight at room temperature, the vessel was cooled while the complex was hydrolyzed with excess 10% sulfuric acid. To complete the hydrolysis of the ketimine salt, the ether solvent was distilled off through an inverted Friedrichs condenser, and the residue heated on the water bath for 20 min. The resultant yellow oily layer was extracted with ether. After washing and drying, fractionation of the product gave unreacted benzonitrile and unreacted 8-fluorooctyl chloride (1.4 g.), followed by 8-fluorooctyl phenyl ketone (10.5 g., 70%).

The *2,4-dinitrophenylhydrazone* was recrystallized from ethanol as small red plates.

The solid distillation residue (2 g.) was recrystallized from carbon tetrachloride, giving colorless plates of 1,8-dibenzoyloctane, m.p. 93–93.6°. (Borsche and Wollemann[28] report m.p. 91–92°.) The dioxime, m.p. 121–123°, was recrystallized from methanol. (Ponzio and Biglietti[29] report m.p. 125–126°; Borsche and Wollemann[28] report m.p. 120–121°.)

(*f*) *9-Fluorononanal.* The Grignard reagent from 8-fluorooctyl chloride (12.0 g., 0.072 mole), ether (70 ml.) and magnesium (3.0 g., 0.124 g. atom) was treated with a solution of triethyl orthoformate (12.0 g., 0.081 mole) in

(27) L. Canonica and T. Bacchetti, *Atti accad. nazl. Lincei, Rend., Classe sci. fis., mat. e nat.*, 10, 479 (1951).

(28) W. Borsche and J. Wollemann, *Ber.*, 44, 3185 (1911).

(29) G. Ponzio and F. Biglietti, *Gazz. chim. ital.*, 64, 861 (1934).

50 ml. of ether. There were no apparent signs of any reaction. After heating under reflux for a total of 6 hr., the reflux condenser was replaced by an inverted Friedrichs condenser and the ether removed. The viscous residue was cooled and treated with 100 ml. of 5*N* hydrochloric acid, thus forming a yellow oily layer. The mixture was warmed on a water bath for 20 min. to complete the hydrolysis of the acetal. The product was extracted with ether, and the extracts were washed successively with water, saturated sodium bicarbonate solution and water. After drying over sodium sulfate, distillation of the product gave two fractions: (*a*) 2 g. (17%) of b.p. 98–103° (9 mm.), which readily formed a yellow, crystalline derivative with 2,4-dinitrophenylhydrazine; and (*b*) 3.3 g. (20%) of b.p. 122–124° (9 mm.), which formed a 2,4-dinitrophenylhydrazone only after prolonged boiling. The residue (5.3 g.), a sweet-smelling, yellow, viscous liquid, was impure sebacaldehyde. Fraction (*b*), thought to be unhydrolyzed acetal, was boiled for 1 hr. with 7% sulfuric acid (25 ml.) and dioxane (12 ml.). Distillation of the hydrolyzate gave two fractions, which had boiling points identical to those of fractions (*a*) and (*b*) above. Combination of the two samples of b.p. 98–103° (9 mm.) followed by several fractionations gave pure 9-fluorononanal (2.9 g., 25%).

The *2,4-dinitrophenylhydrazone* was recrystallized from methanol as long yellow needles.

Acknowledgments. The work described herein was carried out under Contract (DRB X-24) with the Defence Research Board of Canada, to whom grateful acknowledgement is made for financial assistance, and for permission to publish this work. The authors wish also to express their indebtedness to the National Research Council of Canada for the awards of a Fellowship (W.C.H.) and a Bursary (W.J.C.).

LONDON, ONTARIO, CANADA

[CONTRIBUTION FROM THE WILLIAM H. NICHOLS CHEMICAL LABORATORY, NEW YORK UNIVERSITY]

Addition of Ethylenediamine to Methyl Methacrylate and to Acrylonitrile. Reactions of the Adducts

S. CARLTON DICKERMAN AND JULIUS SIMON

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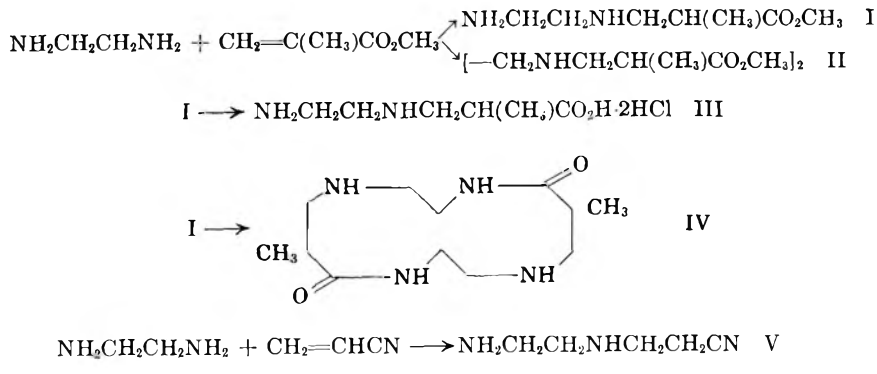
Ethylenediamine has been added to methyl methacrylate and to acrylonitrile. Several diamino esters, diamino acids, and derivatives of these have been prepared. Aged samples of one of the adducts have yielded a substance believed to be 1,5,8,12-tetraza-3,10-dimethyl-2,9-cyclotetradecanedione.

During the course of another investigation certain diamino acids were needed as reference compounds. The simplest representatives of this particular group might be prepared from ethylenediamine and derivatives of acrylic acid. Accordingly such reactions have been studied.

The accompanying flowsheet indicates that both 1:1 and 1:2 adducts, I and II, were obtained from ethylenediamine and methyl methacrylate. The proportions of these adducts were controlled by the ratio of reactants as illustrated in Table I. The formation of adducts which contain only one



molecule of methyl methacrylate per amino group has been observed previously.[1]

TABLE I
PRODUCTS FROM ETHYLENEDIAMINE AND METHYL METHACRYLATE

Run	Moles ED[a] / Moles MM	Yield, % I	Yield, % II
1	6.0	62	—
2	3.0	55, 61	—
3	1.1	47	24
4	1.0	37, 44	28, 28

[a] *ED* = ethylenediamine, *MM* = methyl methacrylate.

Several unsuccessful attempts were made to obtain the 1:1 adduct of ethylenediamine and methyl acrylate by identical procedures. However, these reaction mixtures could not be distilled without decomposition and appeared to be polymeric.[2] Presumably, an explanation of our diverse results with the two acrylates resides in their structural difference. The alpha methyl group would be expected to retard weakly addition by the inductive effect and to retard strongly aminolysis by both inductive and steric effects. The fact that many amines have been added in good yield to both acrylates demonstrates that addition is usually faster than aminolysis. Thus, it is probable that the 1:1 adduct of ethylenediamine and methyl acrylate was formed but that addition was followed by polymeric aminolysis. The observed instability of the adduct I may be offered as evidence for the latter conclusion. Finally, it is important to note that 1:1 adducts of ethylenediamine contain a primary amino group and, in that sense, an excess of amine. Thus, our results should be compared with those of Morsch[3] who showed that adducts of methylamine and methyl acrylate gave amides with excess methylamine.

The desired unsubstituted diamino acid was synthesized by an indirect method. Ethylenediamine was added to acrylonitrile to yield the adduct V which was converted by standard methods into the ester VI and acid VII. At the time these reactions were carried out the 1:2 adduct of ethylene diamine and acrylonitrile was not desired and experimental conditions were selected to minimize its formation. The preparation of both of these adducts has since been reported.[4]

An interesting phase of this work evolved from the observation that the diamino ester I is unstable. Samples of this material, a colorless mobile liquid, gradually thicken and partially crystallize. A colorless solid of m.p. 260–262° was isolated in 4% yield from such aged samples. This substance has been formulated as 1,5,8,12-tetraza-3,10-dimethyl-2,9-cyclotetradecanedione (IV) on the bases of analytical and chemical evidence. The formation of IV from I may be rationalized in terms of intermolecular and intramolecular aminolysis.

EXPERIMENTAL[5]

Methyl 3-(2-aminoethylamino)-2-methylpropanoate (I) *and N,N'-di(2-methoxycarbonyl-2-methylethyl)ethylenediamine* (II). Methyl methacrylate[6] was added to 95–100% ethylenediamine with stirring over a period of 60 to 90 min. The temperature of the reaction mixture was maintained at 30–40° by intermittent cooling. After addition of the acrylate the reaction mixtures were allowed to remain at room temperature for 20 to 24 hr. prior to distillation. The amounts of reactants and the yields of I and II are recorded in Table I.[7] The diamino ester I was obtained as a colorless oil of b.p. 88° at 2.0 mm.

Anal. Calcd. for $C_7H_{16}N_2O_2$: C, 52.5; H, 10.0; N, 17.5. Found: C, 52.7; H, 9.9; N, 17.6.

The dihydrochloride of I was isolated as a colorless, microcrystalline, hygroscopic solid of m.p. 139–141°.

Anal. Calcd. for $C_7H_{18}Cl_2N_2O_2$: Cl, 30.4; N, 12.0. Found: Cl, 30.1; N, 12.1.

The 1:2 adduct II was obtained as a colorless oil of b.p. 125° at 0.1 mm.

Anal. Calcd. for $C_{12}H_{24}N_2O_4$: C, 55.3; H, 9.2; N, 10.8. Found: C, 55.7; H, 9.0; N, 11.0.

Dihydrochloride of II, m.p. 149–151°.

Anal. Calcd. for $C_{12}H_{26}Cl_2N_2O_4$: N, 8.4. Found: N, 8.2.

Treatment of II with benzenesulfonyl chloride yielded *N,N'-dibenzenesulfonyl-N,N'-di(2-methoxycarbonyl-2-methylethyl)ethylenediamine* of m.p. 140–142° after recrystallization from a mixture of benzene and ligroin.

Anal. Calcd. for $C_{24}H_{32}N_2O_8S_2$: N, 5.2. Found: N, 5.2.

3-(2-Aminoethylamino)-2-methylpropanoic acid dihydrochloride (III). The diamino ester I (3.00 g.) was dissolved in 15 ml. of 12% hydrochloric acid and the solution was heated on the steam bath for 3 hr. Evaporation under reduced pressure gave a syrup which was crystallized from ethanol to yield 2.00 g. (46%) of III. After recrystallization from the same solvent III was isolated as colorless needles of m.p. 179–181°.

Anal. Calcd. for $C_6H_{16}Cl_2N_2O_2$: Cl, 32.4; N, 12.8. Found: Cl, 32.3; N, 12.7.

The benzoyl derivative of III was prepared from I by a Schotten-Baumann reaction, which gave an oil, followed by refluxing for 2 hr. in 5% sodium carbonate solution. Acidification of the alkaline solution yielded a mixture of oil and solid. The solid, benzoic acid, was dissolved in ether leaving the oil which was dissolved in benzene and crystallized by the addition of petroleum ether. After recrystallization from a mixture of benzene and ethanol, *N,N'-dibenzoyl-3-(2-aminoethylamino)-2-methylpropanoic acid* was isolated as colorless needles of m.p. 122–124°.

Anal. Calcd. for $C_{20}H_{22}N_2O_4$: N, 7.9. Found: N, 7.9.

Stability of I. Formation of *1,5,8,12-tetraza-3,10-dimethyl-2,9-cyclotetradecanedione* (IV). Samples of I gradually thickened and began to crystallize after standing for about four days at laboratory temperatures. For about two weeks ethyl ether could be used to dissolve the oil but after that the oil was no longer soluble in ether and ice water or acetone was

(1) D. R. Howton, *J. Org. Chem.*, **10**, 277 (1945).

(2) The preparation of resinous compounds from ethylenediamine and esters of acrylic and methacrylic acids has been reported by G. D. Graves in U. S. Patent 2,146,210.

(3) K. Morsch, *Monatsh.*, **63**, 220 (1933).

(4) A. P. Terent'ev and A. N. Kost, *Zhur. Obshchei Khim.*, **20**, 2069 (1950); *C. A.*, **45**, 5622 (1951).

(5) Melting points are uncorrected. Some of the microanalyses were performed by the Schwarzkopf Microanalytical Laboratory, New York.

(6) Samples of methyl acrylate and methyl methacrylate were generously contributed by the Rohm & Haas Co.

(7) The authors are indebted to Mr. Morton Rezak for repeating several of these reactions.

used. A sample of I (52 g.), which had remained at laboratory temperatures for two months, was stirred with 50 ml. of ice water and filtered to yield 2.1 g. (4%) of colorless needles. After recrystallization from water IV melted from 260–262° with decomposition.

Anal. Calcd. for $C_{12}H_{24}N_4O_2$: C, 56.2; H, 9.4; N, 21.9; neut. equiv., 128; mol. wt., 256. Found: C, 56.6; H, 9.2; N, 21.8; neut. equiv., 129; mol. wt., 234 (Rast), 284 (Barger).

A nitroso derivative of IV was prepared by treating an aqueous solution of the hydrochloride with sodium nitrite. After recrystallization from dimethylformamide the nitroso derivative of IV melted from 255–263° with decomposition.

Anal. Calcd. for $C_{12}H_{22}N_6O_4$: N, 26.7. Found: N, 26.9.

A benzoyl derivative of IV was prepared by the usual procedure and was recrystallized from acetic acid, m.p. 296–298° with decomposition.

Anal. Calcd. for $C_{26}H_{32}N_4O_4$: N, 12.1. Found: N, 11.9.

2-(2-Aminoethylamino)propanenitrile (V). Acrylonitrile (10.6 g., 0.20 mole) was added dropwise with stirring, over a period of 90 min., to 36.0 g. (0.60 mole) of ethylenediamine. The mixture was allowed to stand at room temperature overnight and was then distilled under reduced pressure to yield 13.4 g. (59%) of V, b.p. 124–127° at 10 mm. (reported[4] 101° at 1.5 mm.).

Anal. Calcd. for $C_5H_{11}N_3$: neut. equiv., 56.6. Found: neut. equiv., 57.9.

The dihydrochloride of V was prepared in ethanol by the addition of ethanolic hydrogen chloride. After recrystallization from ethanol the salt was isolated as colorless, hygroscopic needles of m.p. 129–131° (reported[4] only that this substance is a very hygroscopic solid).

Anal. Calcd. for $C_5H_{13}Cl_2N_2$: Cl, 38.1; N, 22.6. Found: C, 38.2; N, 22.9.

The benzoyl derivative of V was prepared in the usual manner and was obtained initially as an oil. A benzene solution of the oil was concentrated and the derivative crystallized by the addition of ligroin. After several recrystallizations from benzene, *N,N'-dibenzoyl-3-(2-aminoethylamino) propanenitrile* was isolated as a colorless solid of m.p. 96–98° (a monobenzoyl derivative has been reported[4]).

Anal. Calcd. for $C_{19}H_{19}N_3O_2$: N, 13.1. Found: N, 13.0.

Ethyl 3-(2-aminoethylamino) propanoate dihydrochloride (VI). The amino nitrile V (1.00 g.) was added dropwise to 10 ml. of absolute ethanol saturated with dry hydrogen chloride. After the addition of 0.2 ml. of water the mixture was tightly stoppered and left at room temperature overnight. After heating under reflux for 5 hr. the mixture was filtered hot and on cooling the filtrate deposited 0.79 g. (38%) of VI as very hygroscopic, colorless plates of m.p. 152–154° with previous softening.

Anal. Calcd. for $C_7H_{18}Cl_2N_2O_2$: N, 12.0. Found: N, 12.2.

3-(2-Aminoethylamino)propanoic acid dihydrochloride (VII). The ester dihydrochloride VI (1.000 g.) was dissolved in 10 ml. of dilute hydrochloric acid and the solution was refluxed for 90 min. Evaporation under reduced pressure gave a solid which was recrystallized from ethanol to yield 0.668 g. (76%) of VII as tiny, colorless plates, m.p. 153–155° with previous softening.

Anal. Calcd. for $C_5H_{14}Cl_2N_2O_2$: Cl, 34.6; N, 13.7. Found: Cl, 34.4; N, 13.8.

A sample of VII was converted to the dibenzoyl derivative in the usual manner. After recrystallization from a mixture of benzene and ethanol, *N,N'-dibenzoyl-3-(2-aminoethylamino)propanoic acid* was obtained as clusters of thin, colorless needles of m.p. 149–151° with previous softening at 145°.

Anal. Calcd. for $C_{19}H_{20}N_2O_4$: N, 8.2. Found: N, 8.1.

NEW YORK 53, N. Y.

[CONTRIBUTION NO. 443 FROM THE RESEARCH LABORATORIES OF HOFFMANN-LA ROCHE, INC.]

Pyridindene Derivatives. III. Synthesis from Arecoline

JOHN T. PLATI, ARTHUR K. INGBERMAN,[1] AND WILHELM WENNER

Received September 17, 1956

Two racemic forms of 1-methyl-3-carbomethoxy-4-phenylpiperidine have been obtained from the reaction of phenylmagnesium bromide with arecoline. The two racemic acids were cyclized to the same 2-methyl-2,3,4,4a,9,9a-hexahydro-9-keto-1-pyridindene (VIII).

Treatment with lithium phenyl gave the 9-hydroxy-9-phenyl compound (IX), which was converted into the 9-chloro derivative. The latter was dehydrohalogenated to 2-methyl-9-phenyl-2,3,4,9-tetrahydro-1-pyridindene (XII).

Our earlier work on derivatives of pyridindene has been extended with the objective of devising a synthesis independent of the earlier route.[2] We hoped that this synthesis would allow us to prepare a larger number of derivatives and at the same time serve as an independent confirmation of the structure.

Accordingly, the preparation of 1-methyl-3-carboxy-4-phenyl-piperidine (IV) was investigated as a starting material for the compound XII. Koelsch[3] obtained compound IV by a series of reactions involving a Michael condensation of ethyl cyanoacetate and ethyl cinnamate, reduction over Raney nickel to give the piperidone I, reduction of the carbonyl group with sodium and butanol, and finally N-methylation with formaldehyde. Although the process is feasible, considerable technical difficulty is involved, especially in the reduction with sodium. Other methods of reduction were tried and some limited success was obtained with the copper chromite catalyst.[4] This catalyst in the presence of methanol not only reduced the carbonyl group but simultaneously led to the methylation of the nitrogen, resulting in the ester III (R = ethyl). Hydrolysis of this ester yielded a free acid, which proved to be identical with the acid obtained by the

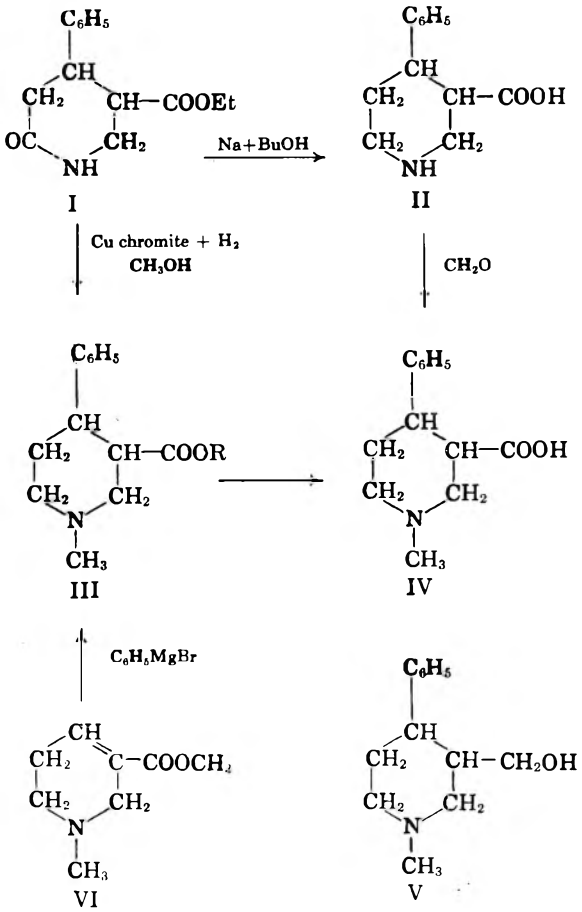
(1) Present address, Bakelite Co., Bound Brook, N. J.

(2) J. T. Plati and W. Wenner, *J. Org. Chem.*, 20, 1412 (1955).

(3) C. F. Koelsch, *J. Am. Chem. Soc.*, 65, 2459 (1943).

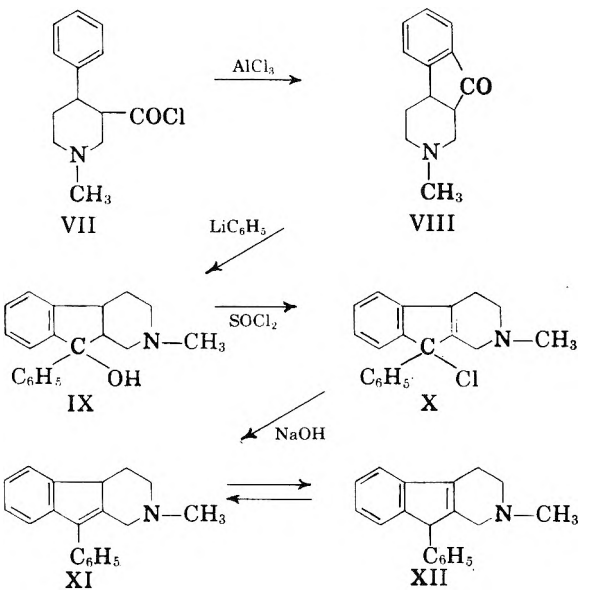
(4) H. B. Adkins, *Reactions of Hydrogen*, The University of Wisconsin Press, Madison, Wis., 1944, p. 13.

Koelsch procedure. However, the yield in the copper chromite reduction was low. This low yield was due in part to further reduction of the ester group with formation of the carbinol V.



Our attention was then directed to an investigation of the reaction of arecoline (VI) with phenylmagnesium bromide. Two racemic methyl esters of structure III (R = CH_3) were obtained as a result of 1,4-addition. These were arbitrarily designated as belonging to an α- and to a β-series corresponding to the two theoretically possible racemic forms. Hydrolysis of the esters gave the corresponding acids (IV). The acid belonging to the α-series was identical with that obtained by the copper chromite reduction as well as by the Koelsch process. The acid from the β-series was obtained in considerably greater yield.

Both of the stereoisomeric acids (IV) were converted by means of thionyl chloride into their respective acid chlorides (VII), which were not isolated but were cyclized by means of aluminum chloride to the same azafluorenone (VIII). Treatment of this latter compound with lithium phenyl gave the expected product, the tertiary alcohol (IX). Further reaction with thionyl chloride gave a product, presumably the chloro derivative (X) which gave the desired 2-methyl-9-phenyl-2,3,4,9-tetrahydro-1-pyridindene (XII) after stirring with alkali. Its identity was established beyond doubt not only by its physical properties but also by the preparation of a thiocyanate and by its characteristic isomerization to 2-methyl-9-phenyl-2,3,4,4a-tetrahydro-1-pyridindene (XI), isolated as a nitrate.[2]



Thus, it is evident that the above process lends itself to the preparation of a large variety of pyridindenes since three different reagents can be varied, namely, the unsaturated piperidine, the Grignard reagent, and the organolithium compound.

EXPERIMENTAL

All melting points are uncorrected.

Reduction of 5-carbethoxy-4-phenyl-2-piperidone (I) *with copper chromite catalyst in methanol. 1-Methyl-3-hydroxymethyl-4-phenylpiperidine* (V). A mixture of 30 g. of 5-carbethoxy-4-phenyl-2-piperidone (I),[3] 176 cc. of methanol, and 12 g. of copper chromite catalyst[4] was hydrogenated for 3.5 hr. at 3000 lb. at 160–200°. The mixture was filtered and the solvent removed at diminished pressure. The residue was then fractionally distilled and separated into two fractions, one fraction weighing 2.8 g. and boiling at 76–90° at 0.6 mm. and a second fraction weighing 32.7 g. and boiling at 125–127° at 0.6 mm.

The second fraction was dissolved in 100 cc. of petroleum ether (b.p. 30–75°) and permitted to crystallize. The crystals were filtered and dried in a dry air stream at 50°. The yield was 12.6 g. of material melting at 104–106°. After recrystallization from ethyl acetate the compound melted at 107–109°.

Anal. Calcd. for $C_{13}H_{19}NO$: C, 76.05; H, 9.33; N, 6.82; neut. equiv., 205. Found: C, 75.96; H, 9.60; N, 6.72; neut. equiv., 204.

1-Methyl-3-carbethoxy-4-phenylpiperidine (III, R = Et) (*α-series*). The petroleum ether filtrate from above was distilled to dryness and the residue was dissolved in ether. The ether solution was treated with dry hydrogen bromide gas to give 23.0 g. of the crude hydrobromide. After two crystallizations from alcohol and drying in a vacuum desiccator over potassium hydroxide, a melting point of 206–207.5° was obtained for the pure hydrobromide.

Anal. Calcd. for $C_{15}H_{21}NO_2 \cdot HBr$: C, 54.88; H, 6.76; Br, 24.35. Found: C, 54.43; H, 6.58; Br, 24.41.

The free base was obtained from the aqueous solution of the hydrobromide by adding 50% potassium carbonate

below 15° and extracting with ether. The ether was distilled off on the steam bath, and the residual oil was then distilled. On distillation, a material boiling at 125–126°/0.15 mm., $n_D^{19.5}$ 1.5159, was obtained.

1-Methyl-3-carboxy-4-phenylpiperidine hydrochloride (IV) (*α-series*). A mixture of 10 g. of 1-methyl-3-carbethoxy-4-phenyl piperidine base and 50 cc. of constant boiling hydrochloric acid was distilled through a packed column of approximately 12 theoretical plates until the distillation temperature rose to 110°. After distilling at 110° for about 30 to 40 min. the mixture was distilled to dryness *in vacuo* and the residue dried overnight in a vacuum desiccator with potassium hydroxide. An amorphous white powder weighing 10.3 g. was thus obtained. When one gram of this amorphous powder was dissolved in 3 cc. of alcohol, 0.85 g. of pure product, m.p. 219–221° was obtained. This melting point agrees with that of the compound described by Koelsch.[3]

Reaction of arecoline (VI) *with phenylmagnesium bromide.* To a mixture of 38 g. of arecoline (VI) hydrobromide (0.16 mole) and 30 cc. of water was added 25 cc. of 50% potassium carbonate (by weight) with cooling. The mixture was extracted with 100 cc. of benzene five times. At the end of the second and third extractions, an additional charge of potassium carbonate solution was added. Thus, a total of 75 cc. of potassium carbonate solution and 500 cc. of benzene was used. The combined benzene extracts were dried with sodium sulfate, and the benzene removed *in vacuo*. The residue weighed 25 g. and represented the arecoline base.

Into a 500-cc. three-necked flask were placed 7.94 g. (0.33 gram atom) of magnesium turnings and about 100 cc. of dry ether. A solution of 50.5 g. (0.32 mole) of bromobenzene in 100 cc. of ethereal solution was added in the course of an hour to maintain gentle reflux. After stirring for 30 min. the mixture was cooled to −10°, and 65 cc. of an ether solution of the arecoline base was added during the course of one hr. The mixture was stirred for 20 min. longer at the same temperature, poured into cracked ice, and then treated slowly with 160 cc. of ice cold 6*N* hydrochloric acid The aqueous layer was separated, extracted with 200 cc. of ether, and then treated with cooling in an ice bath with 200 cc. of 50% potassium carbonate (by weight). The mixture was extracted with 400 cc. of ether, and the ethereal layer was separated by centrifuging. The aqueous layer containing insoluble magnesium hydroxide was extracted with 350 and 250 cc. of ether. The combined ether extracts were dried with sodium sulfate, and after removing the ether, the residue was distilled. In this manner, 27.7 g (73%) of oil boiling mostly at 124–128° at 0.5 mm. was obtained. This oil represented a mixture of the two stereoisomeric forms of 1-methyl-3-carbomethoxy-4-phenyl piperidine. These isomers may be conveniently designated as belonging to an α- and a β- series.

Anal. Calcd. for $C_{14}H_{19}NO_2$: Neut. equiv., 233. Found: Neut. equiv., 232.

1-Methyl-3-carbomethoxy-4-phenylpiperidine (III, R = Me) *hydrobromide* (*α- series*). The ester mixture from above was dissolved in about 1 liter of ether, and hydrogen bromide gas was introduced. The precipitate was crystallized from 150 cc. of methanol to give 8.15 g. of crystals, m.p. 204–207°. The melting point was raised to 214–217° by recrystallization from ethyl alcohol. This compound represents the pure hydrobromide of one of the stereoisomeric forms of 1-methyl-3-carbomethoxy-4-phenyl piperidine (III, R = Me) which will be referred to as belonging to the α- series.

Anal. Calcd. for $C_{14}H_{19}NO_2 \cdot HBr$: C, 53.51; H, 6.42. Found: C, 53.63; H, 6.36.

1-Methyl-3-carbomethoxy-4-phenylpiperidine (III, R = Me) (*α- series*). To a mixture of 8.09 g. of the above hydrobromide and 50 cc. of water was added with cooling 8 cc. of 50% potassium carbonate (by weight). The mixture was extracted twice with 25 cc. of ether, and the ether solution was dried with sodium sulfate. Distillation gave 5.44 g. of free α- ester, b.p. 100° at 0.2 mm., $n_D^{24.6}$ 1.5188.

Hydrolysis to 1-methyl-3-carboxy-4-phenylpiperidine (IV) *hydrochloride* (*α-series*). To this base were added 11 cc. of water and 15 cc. of concentrated hydrochloric acid, and the mixture was distilled slowly during 25 min. until no more methanol distilled over. After distilling off the solvent *in vacuo* in a bath which was gradually brought to 85°, the residue was crystallized from 15 cc. of ethanol. In this manner, 4.57 g. of 1-methyl-3-carboxy-4-phenyl-piperidine (IV) hydrochloride, m.p. 214–216°, was obtained. This material crystallized in prisms and was identical in appearance with the material obtained through the copper chromite reduction. It showed no depression in melting point when mixed with this substance.

1-Methyl-3-carbomethoxy-4-phenylpiperidine (III, R = Me) *oxalate* (*β-series*). The methanol filtrate from the crystallization of the crude hydrobromide mixture was distilled to dryness *in vacuo*. The residue weighed 19.8 g. and melted at 166–168°. This material plus an additional amount from another experiment, making a total of 23.4 g., was treated with cooling with 90 cc. of 10% sodium carbonate and extracted with 150, 100, and 100 cc. portions of ether. The ether extracts were treated with a saturated solution of oxalic acid in ether until no further precipitation occurred, and the crude precipitate was crystallized from 150 cc. ethyl alcohol. In this manner, 18.2 g. of the oxalate of the β-ester, m.p. 157–158° was obtained.

Anal. Calcd. for $C_{14}H_{19}NO_2 \cdot C_2H_2O_4$: C, 59.43; H, 6.55. Found: C, 59.23; H, 6.26.

1-Methyl-3-carbomethoxy-4-phenylpiperidine (III, R = Me) (*β-series*). To a solution of 18.3 g. of the oxalate, m.p. 157–158°, in 150 cc. of water was added 50 cc. of 50% potassium carbonate. A solid base was precipitated. This was extracted with 100 cc. of ether, and the ether solution was dried with sodium sulfate and distilled at 100–110° and 0.25 mm. A yield of 12.0 g. of distillate was obtained which later solidified in the receiver. The 1-methyl-3-carbomethoxy-4-phenyl-piperidine of the β- series, thus obtained, melted at 55–58°.

1-Methyl-3-carboxy-4-phenylpiperidine (IV) *hydrochloride* (*β-series*). A mixture of 12.0 g. of the above β-ester, 33 cc. of water and 44 cc. of concentrated hydrochloric acid was distilled through a 12-plate column over a period of about 30 min. until methanol no longer came over. The mixture was distilled to dryness *in vacuo* in a bath, which was gradually brought to 80°. The residue was crystallized from 40 cc. of hot ethyl alcohol to give 14.3 g. of platelike crystals, melting at 212–213°. The yield and the analysis indicate that the substance contains a molecule of alcohol of crystallization. The substance gives a distinct depression in melting point when mixed with the corresponding substance from the α-series. The hygroscopic nature of the compound as well as the alcohol of crystallization presented some difficulty in the analysis. The compound was dried *in vacuo* at room temperature first over potassium hydroxide for about 20 hr. and then over P_2O_5 for several hours. The following data were obtained.

Anal. Calcd. for $C_{13}H_{17}NO_2 \cdot HCl \cdot C_2H_5OH$: C, 59.69; H, 8.02; C_2H_5O, 14.93. Found: C, 59.85; H, 8.15; C_2H_5O, 14.31.

An ethoxyl value of 1.71% was found even after drying *in vacuo* at 100° over P_2O_5.

2-METHYL-2,3,4,4a,9,9a-HEXAHYDRO-9-KETO-1-PYRIDINDENE (VIII)

From the α-series. To 7.25 g. of 1-methyl-3-carboxy-4-phenyl-piperidine (IV) hydrochloride (α-series) was added 50 cc. of thionyl chloride. Complete solution occurred. After standing at room temperature for 2 hr., the thionyl chloride was distilled off at diminished pressure below 50°. To the yellow residue was added 100 cc. of anhydrous tetrachloroethane. After stirring for a short time the yellow

residue went into solution and the resulting solution was again subjected to distillation at diminished pressure until 50 cc. of distillate was obtained. To the residual solution was added 50 cc. more of tetrachloroethane. The solution was warmed to 40° with stirring and 4 g. of anhydrous aluminum chloride added. No hydrogen chloride was liberated. Five more grams of anhydrous aluminum chloride was then added. A vigorous evolution of hydrogen chloride commenced. After complete addition of the second batch of anhydrous aluminum chloride, the reaction mixture was permitted to stir for one more hour at 40°. The reaction mixture was poured into 300 g. of ice and 25 cc. of concentrated hydrochloric acid. After standing overnight the organic and aqueous layers were separated. The tetrachloroethane layer was extracted once more with 20 cc. of water and then discarded. The combined aqueous liquors were extracted once with ether, cooled to 15°, and made strongly alkaline with 50% sodium hydroxide. The resulting mixture was then extracted once with 150 cc. of ether and then three times more with 25 cc. of ether. The combined ether extracts were dried over sodium sulfate and concentrated on the steam bath. The residue was then distilled at diminished pressure to give 5.1 g. of material boiling at 120° at 0.15 mm. This corresponds to 88% of the theoretical yield. The distillate after standing a short time crystallized and melted at 64.5–65.5°. One gram of the above distillate was dissolved in 50 cc. of dry ether, and dry hydrogen bromide gas was introduced. The precipitate was filtered and crystallized from 7 cc. of ethanol. The crystals of 2-methyl-2,3,4,4a,9,9a-hexahydro-9-keto-1-pyridindene (VIII) hydrobromide weighed 1.2 g. and melted at 208–210°. It was crystallized once more and analyzed.

Anal. Calcd. for $C_{13}H_{15}NO\cdot HBr$: C, 55.33; H, 5.71. Found: C, 55.27; H, 5.40.

From the β-series. To 40 g. (0.13 mole) of 1-methyl-3-carboxy-4-phenyl piperidine (IV) hydrochloride containing alcohol of crystallization (β-series) was added, with cooling and stirring, 160 cc. of thionyl chloride. After standing at room temperature for 3.5 hr., the thionyl chloride was removed at reduced pressure in a bath which was gradually heated to 60°. To the residue, 250 cc. of tetrachloroethane was added, and 50 cc. was distilled at reduced pressure in order to remove traces of thionyl chloride. During 45 min., 50 g. (0.37 mole) of aluminum chloride was added at 40° in a bath maintained at about 38°. The mixture was stirred for an additional 30 min. and poured into 400 g. of ice and 50 cc. of concentrated hydrochloric acid. The aqueous layer was separated, extracted with 100 cc. of ether, and with cooling below 15°, treated with 300 cc. of 30% sodium hydroxide. The organic base was extracted with 200- and 100-cc. portions of ether. After drying with sodium sulfate, the ether was removed and the residue distilled. At about 127° and 0.3 mm., 19.8 g. (74%) of 2-methyl-2,3,4,4a,9,9a-hexahydro-9-keto-1-pyridindene (VIII) was obtained. The material solidifies in the receiver. It turns brown on standing.

The hydrobromide was prepared by passing hydrogen bromide gas into a solution of one gram of the ketone in 50 cc. of ether. The precipitate was digested with 20 cc. of hot acetone, cooled, and filtered. In this manner, 1.12 g. of the almost pure hydrobromide, m.p. 204–207° was obtained. Further crystallization from ethyl alcohol raised the melting point to 208–211°. A mixed melting point with the product from the α- series (part IIIA), gave no depression.

Anal. Calcd. for $C_{13}H_{15}NO\cdot HBr$: C, 55.32; H, 5.72. Found: C, 55.09; H, 5.48.

A sample of the hydrobromide was dissolved in a little water, and dilute sodium hydroxide was added. The *free base* thus precipitated melted at 64–65°. In a mixed melting point determination with the base prepared in a similar manner from the α- series, no depression was noted.

2-Methyl-2,3,4,4a,9,9a-hexahydro-9-hydroxy-9-phenyl-1-pyridindene (IX). In a 1-l. 3-necked flask provided with stirrer and condenser was placed about 200 cc. of dry ether and 1.17 g. (0.170 g.-atom) of lithium wire cut in small pieces. During a period of 1 hr., 60 cc. of an ether solution containing 13.1 g. (0.083 mole) of bromobenzene was added to maintain gentle reflux. After stirring for 2 hr. more to complete the formation of the lithium phenyl, the mixture was cooled in an ice bath to 3° and a solution of 16.7 g. of 2-methyl-2,3,4,4a,9,9a-hexahydro-9-keto-1-pyridindene (VIII) in about 65 cc. of dry ether was added in 40 min. at 3–5°. The mixture was stirred for an additional 22 min. in the ice bath, and then the ice bath was removed, and stirring continued for 1.5 hr. A white solid was gradually precipitated.

The mixture was again cooled in the ice bath, and 53.4 cc. of 3.18*N* sulfuric acid in 150 cc. of water was added slowly. In order to neutralize the excess acid, 33.7 cc. of 2.48*N* sodium hydroxide was added, and the ether layer was separated. To insure complete separation of the base, the aqueous layer was reated with 40 cc. of 50% potassium carbonate and extracted with 100 cc. of ether. The combined ether solutions were dried with sodium sulfate and treated with a saturated ethereal solution of oxalic acid. The precipitate was crystallized from 100 cc. of methanol to give 10.6 g. of crystals, melting at 208–210° with effervescence. For analysis, a sample was crystallized but the melting point remained unchanged. This substance represents the *oxalate* of 2-methyl-2,3,4,4a,9,9a-hexahydro-9-hydroxy-9-phenyl-1-pyridindene. An additional 2.13 g. of oxalate was obtained from the mother liquor.

Anal. Calcd. for $C_{19}H_{21}NO\cdot C_2H_2O_4$: C, 68.28; H, 6.28; neut. equiv., 369. *Found:* C, 68.13; H, 6.39; neut. equiv., 371.

Free base. A hot solution of 8.2 g. of the oxalate in 200 cc. of water was cooled to room temperature and 30 cc. of 10% sodium hydroxide was added. The gummy precipitate, first obtained, gradually hardened and it was crushed and filtered. It weighed 6.07 g. on drying and melted at 90–92°. A sample was crystallized from dilute alcohol. It melted at 91–93°.

Anal. Calcd. for $C_{19}H_{21}NO$: C, 81.68; H, 7.57. Found: C, 81.44; H, 7.34.

Dehydration of 2-methyl-2,3,4,4a,9,9a-hexahydro-9-hydroxy-9-phenyl-1-pyridindene (IX). *2-Methyl-9-phenyl-2,3,4,9-tetrahydro-1-pyridindene* (XI). To 1 g. of the hydroxy compound (IX) was added with cooling about 10 cc. of thionyl chloride, and the mixture was allowed to stand for 1.5 hr. The thionyl chloride was removed at reduced pressure below 50°, and to the residue was added 10 cc. of 10% sodium hydroxide. After shaking for a few minutes, 5 cc. of ethyl alcohol and 5 cc. of concentrated ammonium hydroxide were added. The mixture was seeded and allowed to stand overnight. The solid which was obtained was crystallized from dilute acetone to give 0.25 g. of crystals melting at 82–84°. Another crystallization gave 0.15 g. of crystals melting at 89–90°, which had the same ultraviolet absorption spectrum as an authentic sample of 2-methyl-9-phenyl-2,3,4,9-tetrahydro-1-pyridindene[2] and showed no depression in a mixed melting point determination.

2-Methyl-9-phenyl-2,3,4,9-tetrahydro-1-pyridindene thiocyanate salt. To 1 g. of the hydroxy compound (IX) was added with cooling 10 cc. of thionyl chloride. After standing overnight at room temperature, 10 cc. of 10% sodium hydroxide was added. After a few minutes shaking during which heat was evolved, 5 cc. of ethyl alcohol was added. After standing for 2 hr. at room temperature, 5 cc. of concentrated ammonium hydroxide was added, and the mixture was agitated mechanically for 3 hr. On standing overnight, the precipitate was filtered, washed with water, and dissolved in a small excess of dilute hydrochloric acid. Dilute sodium hydroxide was added to bring the *p*H to about 6–7. At this point this solution was diluted to 20 cc. and divided into two 10-cc. portions. To one of these 10-cc. portions was added a solution of 3 g. of potassium thiocyanate in 3 cc. of water. After standing for 30 min. the oily precipitate was crystallized in an atmosphere of nitrogen from about 5 cc. of ethanol. In this manner, 0.30 g. of a thiocyanate, m.p.

191–192°, was obtained. The crystalline appearance and the melting point are substantially those of 2-methyl-9-phenyl-2,3,4,9-tetrahydro-1-pyridindene thiocyanate.[2]

Nitrate of 2-methyl-9-phenyl-2,3,4,4a-tetrahydro-1-pyridindene (XI). To the other 10-cc. portion mentioned above was added a supercooled solution of 3 g. of potassium nitrate in 5 cc. of water. After 30 min., the supernatant liquor was decanted from the oily precipitate which was digested for a few minutes with about 5 cc. of hot acetone. After standing for about 3 hr. at room temperature, the mixture was filtered. In this manner, 0.30 g. of solid, m.p. 173–175°, was obtained. After crystallization from ethanol, 0.185 g. of crystals melting at 176–179°, were obtained. The compound was further identified by its absorption spectrum as the nitrate of 2-methyl-9-phenyl-2,3,4,4a-tetrahydro-1-pyridindene (XI).[2]

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NUTLEY, N. J.

[CONTRIBUTION FROM THE W. A. NOYES LABORATORY OF CHEMISTRY, UNIVERSITY OF ILLINOIS]

Nitrogen Compounds of the Phosphoric and Phosphonic Acids. III. Preparation and Properties of Amides of Phenylphosphonic and Phenylphosphonothioic Acids[1]

WILLIAM C. SMITH[2,3] AND L. F. AUDRIETH

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Phenylphosphonic diamide, $C_6H_5PO(NH_2)_2$ (I), and the thioic diamide, $C_6H_5PS(NH_2)_2$ (II), can be prepared readily by interaction of the respective chlorides with liquid ammonia. Partial alcoholysis of (I) leads to formation of the alkyl P-phenylphosphonamidates, $C_6H_5PO(NH_2)(OR)$, where R = C_2H_5, n-C_3H_7, n-C_4H_9, and n-C_5H_{11}. Partial hydrazinolysis of (I) gives the phenylphosphonamidic hydrazide, $C_6H_5PO(NH_2)(N_2H_3)$, which reacts with p-methoxybenzaldehyde and with acetone to form the respective N^2-arylidene(alkylidene)phenylphosphonamidic hydrazides.

Only a limited number of unsubstituted amides of P-alkyl or -arylphosphonic acids have been described in the literature[4,5] and only one of the corresponding thioic compounds has been reported.[6] A convenient method for preparing phenylphosphonic diamide (I), and the previously unknown phenylphosphonothioic diamide (II) is given in the present paper. A new type of reaction by which alkyl P-phenylphosphonamidates, $C_6H_5PO(NH_2)OR$, are obtained by the alcoholysis of (I) is also described. The preparation of phenylphosphonamidic hydrazide by the hydrazinolysis of (I) is also discussed.

Both phenylphosphonic diamide (I) and phenylphosphonothioic diamide (II) were prepared in excellent yields by interaction of the corresponding dichlorides with liquid ammonia. It was found that (II) is much less stable toward hydrolysis than the oxo-analog.

The partial alcoholysis of (I) with ethyl, n-propyl, n-butyl, and n-amyl alcohols resulted in the formation of a new class of compounds that may be designated as alkyl P-phenylphosphonamidates, $RPO(NH_2)(OR)$ (III to VI, respectively). The compounds are solids that can be purified readily by recrystallization. There was no marked tendency for further alcoholysis to the ester to take place. The time required for reaction decreased with increasing molecular weight of the alcohol employed, presumably due in large measure to the progressively higher reaction temperature attained.

Hydrazinolysis of (I) gave phenylphosphonamidic hydrazide (VII), $C_6H_5PO(NH_2)N_2H_3$, in moderate yield. No phenylphosphonic dihydrazide was obtained in the reaction. The identity of (VII) was confirmed (*a*) by cryoscopic studies in water, (*b*) by the determination of the percentage of nitrogen present as hydrazine nitrogen, and (*c*) by conversion into aldehyde and ketone derivatives.

EXPERIMENTAL[7,8]

Phenylphosphonic diamide (I), $C_6H_5PO(NH_2)_2$. Attempts to prepare (I) by the method of Michaelis,[9] based upon the reaction of the acid chloride with concentrated aqueous

(1) For the second article of this series see Smith, Gher, and Audrieth, *J. Org. Chem.*, **21**, 113 (1956).

(2) Abstracted from doctoral dissertation submitted to the Graduate College of the University of Illinois by W. C. Smith (1954).

(3) Victor Chemical Works Research Fellow at the University of Illinois, 1953–4; present address, Chemical Department, E. I. du Pont de Nemours and Company, Inc., Wilmington, Del.

(4) Kosolapoff, *Organophosphorus Compounds*, John Wiley and Sons, Inc., New York, N. Y., 1950.

(5) Rätz, *J. Am. Chem. Soc.*, **77**, 4170 (1955).

(6) Michaelis, *Ann.*, **315**, 43 (1901).

(7) The analytical values for the percentage of carbon were outside experimental error in several instances, even though the other analytical values were quite satisfactory. Despite repeated efforts by Mr. J. Nemith, to whom the authors are grateful for carrying out microanalyses of compounds described in this and previous articles of this series, no method for attaining more acceptable values could be developed.

(8) Melting points are uncorrected.

(9) Michaelis, *Ann.*, **293**, 193 (1896).

ammonia, yielded only small amounts of the desired product. The desired compound was obtained in excellent yield, however, when liquid ammonia was employed. Phenylphosphonic dichloride[10] (97.5 g., 0.500 mole) was added dropwise with vigorous stirring, over a 1-hr. period, to 1 l. of liquid ammonia contained in a Dewar flask. A loose-fitting, plastic cover containing holes for the funnel tip and the stirrer shaft was placed over the flask to prevent spattering. The crude product was separated from the liquid ammonia mother liquor by filtration and the solid washed with two 100-ml. portions of liquid ammonia. The ammonia-insoluble solid was found to consist of essentially pure (I), melting sharply at 188°, and comprised the larger part of the yield of the desired reaction product. A few additional grams of (I) were obtained by evaporating the ammonia mother liquor to dryness, extracting the ammonium chloride with water, and recrystallizing the water-insoluble material from absolute ethanol. Recrystallization from water gave (I) that was suitable for use as a starting material for subsequent work (m.p. 188°C.); pure (I) melting at 191°C. could be obtained by recrystallization from absolute ethanol. The yield was 73.3 g. (94.1%).

Anal. Calcd. for $C_6H_9N_2OP$: C, 46.16; H, 5.81; N, 17.95. Found: C, 45.84; H, 5.76; N, 17.97.

Quantitative solubilities of (I) in g./100 g. of solvent at 25° were determined: water, 1.11; absolute ethanol, 0.392; diethyl ether, 0.006; chloroform, 0.011; carbon tetrachloride, 0.0025.

The attempted titration of (I) with 1*N* hydrochloric acid demonstrated that the compound was not sufficiently basic to form a salt when treated with a strong acid. An aqueous solution of (I) had a *p*H of 7.10. Treatment of an ethanolic solution of (I) with hydrogen chloride gas resulted in the cleavage of the P—N bond and the precipitation of ammonium chloride. Addition of (I) to 1*N* sodium hydroxide brought about the slow hydrolysis of the amide.

Phenylphosphonothioic diamide (II), $C_6H_5PS(NH_2)_2$. This compound, like its oxo-analog, could not be prepared by the reaction of the acid chloride with concentrated aqueous ammonia but could be made satisfactorily when liquid ammonia was employed. Phenylphosphonothioic dichloride[10] (106 g., 0.500 mole) was added slowly to one liter of liquid ammonia. The resulting ammonia solution was evaporated to dryness under a stream of dry nitrogen and the crude product extracted with one liter of warm diethyl ether. A portion of crude (II) was recovered by filtration after cooling the ether extract to 0°; the ether mother liquor was then used for two further extractions and subsequently concentrated to recover an additional small quantity of solid. Final recrystallization from ether gave plates melting at 41°. The yield was 72.2 g. (83.7%).

Compound (II) is very soluble in absolute ethanol. It dissolves in water readily with the concomitant formation of an oil that could not be crystallized. It was observed that (II) is quite unstable and that it is particularly sensitive to moisture. It decomposes very rapidly on standing in the atmosphere unless all of the diethyl ether is completely eliminated in the vacuum desiccator. However, even analytically pure samples of (II) were converted to gelatinous masses after standing in closed containers for several months. Results obtained on analysis of recrystallized (II) are given below.

Anal. Calcd. for $C_6H_9N_2PS$: C, 41.85; H, 5.27; N, 16.27. Found: C, 41.74; H, 5.55; N, 16.02.

Ethyl P-phenylphosphonamidate (III), $C_6H_5PO(NH_2)$-OC_2H_5. A solution of (I) (10.0 g., 0.0642 mole) in absolute ethanol (400 ml., 6.87 moles) was held at reflux for 24 hr. The amount of ethanol employed was just sufficient to dissolve all of the (I) at the reaction temperature. One hundred ml. of xylene was then added to the alcoholic solution, the unreacted ethanol removed by distillation, and the crude product isolated by cooling the residual xylene solution. After washing the crude (III) with 25 ml. of diethyl ether the product was recrystallized from xylene as a colorless solid melting at 127°. The yield was 9.23 g. (90.1%). The product is soluble in hot absolute ethanol, hot water, chloroform, acetone, and hot xylene; it is moderately soluble in cold ethanol, and only slightly soluble in diethyl ether, cold water, and petroleum ether.

Anal. Calcd. for $C_8H_{12}NO_2P$: C, 51.88; H, 6.53; N, 7.56. Found: C, 52.53; H, 6.38; N, 7.59.

n-Propyl P-phenylphosphonamidate (IV), $C_6H_5PO(NH_2)$-OC_3H_7. A slurry of (I) (10.0 g., 0.0642 mole) in redistilled 1-propanol (50 ml.; 0.668 mole) was heated at reflux for 24 hr. Complete solution occurred after 22 hr.; the temperature reached a maximum of 100° during the reflux period.[11] The bulk of the crude (IV) was isolated by concentrating the alcoholic solution to 40 ml. and cooling it to 0°. A small additional amount of (IV) was precipitated from the mother liquor by treatment with 75 ml. of diethyl ether. The amidate is soluble in absolute ethanol, water, carbon tetrachloride, and xylene, moderately soluble in diethyl ether, and slightly soluble in petroleum ether. Recrystallization of (IV) from carbon tetrachloride gave a colorless solid melting at 135°. The yield was 10.2 g. (74.3%).

Anal. Calcd. for $C_9H_{14}NO_2P$: C, 54.26; H, 7.08; N, 7.03. Found: C, 54.38; H, 6.97; N, 6.94.

n-Butyl P-phenylphosphonamidate (V), $C_6H_5PO(NH_2)$-OC_4H_9. A slurry of (I) (10.0 g., 0.0642 mole) in redistilled 1-butanol (50 ml., 0.547 mole) was held at reflux for 8 hr. During the course of the reaction a maximum temperature of 110° was reached and (I) dissolved slowly. A trace of solid removed from the hot alcoholic solution by filtration was identified by its melting point as unreacted diamide. Crystallization could not be effected by cooling the filtrate; it was therefore concentrated to 40 ml., cooled, and treated with 40 ml. of petroleum ether (b.p. 100–110°). A substantial amount of product precipitated; further concentration of the alcoholic filtrate and treatment with petroleum ether (b.p. 100–110°) yielded several additional crops of crude product. The compound is soluble in absolute ethanol, 1-butyl alcohol, hot water, hot petroleum ether and hot carbon tetrachloride; it is moderately soluble in diethyl ether, slightly soluble in cold carbon tetrachloride or cold petroleum ether, and insoluble in cold water. The pure compound, recrystallized from carbon tetrachloride, melts at 104°. The yield was 11.0 g. (80.5%).

Anal. Calcd. for $C_{10}H_{16}NO_2P$: C, 56.32; H, 7.56; N, 6.57. Found: C, 56.37; H, 7.62; N, 6.32.

n-Amyl P-phenylphosphonamidate (VI), $C_6H_5PO(NH_2)$-OC_5H_{11}. A slurry of (I) (10.0 g., 0.0642 mole) was heated at reflux with *n*-amyl alcohol (50 ml., 0.464 mole) for 7 hr. The diamide dissolved slowly during the reflux period and solution was complete after 6 hr. A maximum temperature of 130° was attained during the reaction; the development of a light brown color indicated that slight decomposition had taken place. As no solid precipitated on cooling to room temperature, the solution was concentrated to 40 ml., treated with 50 ml. of petroleum ether (b.p. 100–110°) and cooled to 0°. The crude (VI) that precipitated was separated by filtration and washed with two 25-ml. portions of diethyl ether. In order to recover additional product from the *n*-amyl alcohol solution, in which the former is appreciably soluble, it was necessary to remove the alcohol; this was accomplished by concentrating the mother liquor to 20 ml., adding 40 ml. of xylene and then again concentrating the solution to a volume of 35 ml. In this way most of the alcohol was removed and an appreciable amount of solid was recovered on cooling. Additional crude (VI) was recovered from the xylene filtrate by adding 50 ml. of petroleum ether (b.p. 100–110°), cooling the solution and filtering off the

(10) The acid chlorides used in this investigation were kindly furnished by the Victor Chemical Works, Chicago, Ill., and were redistilled before use.

(11) A yield of only 40% was obtained if the reflux time was reduced to 12 hr.

solid fractions that formed on standing. The compound is soluble in *n*-amyl alcohol, absolute ethanol, hot petroleum ether, hot xylene, diethyl ether and hot water; it is moderately soluble in cold xylene, slightly soluble in cold petroleum ether and insoluble in cold water. The pure product, recrystallized from petroleum ether (b.p. 100–110°), melts at 82°. The yield was 8.99 g. (61.8%).

Anal. Calcd. for $C_{11}H_{18}NO_2P$: C, 58.11; H, 7.98; N, 6.16. Found: C, 58.48; H, 8.13; N, 6.08.

Phenylphosphonamidic hydrazide (VII), $C_6H_5PO(NH_2)N_2H_3$. 1-Propanol[12] (96.2 ml., 1.29 moles) containing (I) (20.0 g., 0.128 mole) and 95% hydrazine (18.9 g., 0.564 mole; 12% excess) was heated at reflux for 15 hr. The diamide dissolved slowly during the course of the reaction,[13] and the temperature reached a maximum of 99°. The hot solution was filtered, the filtrate cooled in an ice bath and the resultant solid separated.[14] The product, which consisted largely of phenylphosphonamidic hydrazide, $C_6H_5P(O)(NH_2)(N_2H_3)$, had crystallized as well formed monoclinic plates. It was washed on the filter with 200 ml. of diethyl ether, slurried with an additional 400 ml. of ether, and then placed under vacuum for 36 hr. to remove volatile contaminants. The compound is soluble in water, dimethylformamide, and hot absolute ethanol; it is recrystallized most satisfactorily from the latter solvent. The product was found to be slightly soluble in cold absolute ethanol, and is insoluble in chloroform, benzene, carbon tetrachloride, dioxane, diethyl ether, tetrahydrofuran, ethyl acetate, and acetonitrile. A silver mirror is formed when an aqueous solution of (VII) is treated with ammoniacal silver nitrate solution; a positive test for the presence of a reducing agent is also obtained on treatment with an iodine solution.

(12) The reaction with hydrazine could not be carried out in the absence of a solvent. The actual function of the alcohol in this reaction was not determined.

(13) It was found that nearly all of the diamide could be recovered unchanged if the mixture was allowed to reflux for only three hr. Even after 12 hr. a large portion of the starting material could be recovered unchanged.

(14) The alcoholic filtrate from which the phenylphosphonamidic hydrazide had been removed was found to contain *n*-propyl phenylphosphonamidate, $C_6H_5P(O)(OC_3H_7)(NH_2)$ (IV); this was recovered by treating the filtrate with 30 ml. of *n*-amyl alcohol and by then heating the solution carefully until all of the excess hydrazine had been eliminated. Needles of the ester crystallized when the hot solution was cooled; additional product was obtained on allowing the solution to stand. The compound was purified by recrystallization from carbon tetrachloride; its identity was confirmed (*a*) by melting point and (*b*) by comparison of the infrared spectrum with that of an authentic sample of (IV) prepared by the reaction of phenylphosphonic diamide and 1-propanol in the absence of hydrazine, as described in this article.

Melting point determinations in a capillary tube indicated that (VII) melts over a wide range on slow heating but would melt rapidly when immersed in a heating bath at temperatures substantially below those at which final melting occurred when the heating process was slow. These observations were confirmed by studying the behavior of (VII) on the hot stage of a microscope. When the compound is heated slowly beginning at room temperature, it melts over a range from 162–194°; it will melt rapidly when placed on the hot stage at 153° and will melt slowly but completely when placed on the stage at 143°.

Anal. Calcd. for $C_6H_{10}N_3OP$: C, 42.10; H, 5.89; N, 24.55. Found: C, 40.99; H, 5.88; N, 24.59.

The analytical results and the observations that have been recorded above could be applied equally well to a hydrazihydrazidate, with the formula $[C_6H_5PO(N_2H_3)NH—]_2$. This possibility was eliminated (*a*) by determining the molecular weight of (VII) in water, (*b*) by analyzing for "hydrazine" nitrogen, and (*c*) by conversion to representative ketone and aldehyde derivatives, respectively.

The molecular weight of (VII) in water was determined cryoscopically. The determination was made as rapidly as possible in order to lessen errors caused by hydrolysis of the product. The apparent molecular weight values were found to come within 10% of the calculated value for (VII).

Anal. Calcd. for $C_6H_{10}N_3OP$: Mol. wt. 171.2. Found: Mol. wt. 175, 157, 156.

Samples of (VII) were dissolved in hydrochloric acid and titrated with a standard iodate solution using the method described in the first article of this series.[15] Duplicate samples of (VII), weighing 0.1066 g. and 0.1028 g., were found to require 24.71 and 24.10 ml. of 0.025*M* KIO_3, corresponding to 16.27 and 16.44% hydrazine nitrogen. The formula $C_{16}H_{10}N_3OP$ requires 16.35%.

Aldehyde and ketone derivatives [N^2-alkylidene(arylidene)phenylphosphonamidic hydrazides] were prepared by adding the carbonyl compound to a warm ethanolic solution of (VII). The *p*-methoxybenzaldehyde derivative was prepared in 84% yield, m.p. 163° (from chloroform).

Anal. Calcd. for $C_{14}H_{16}N_3O_2P$: C, 58.12; H, 5.58; N, 14.52. Found: C, 58.07; H, 5.64; N, 14.26.

The corresponding acetone derivative[16] was obtained in 79% yield, m.p. 193° (from acetone).

Anal. Calcd. for $C_9H_{14}N_3OP$: C, 51.18; H, 6.68; N, 19.90. Found: C, 51.36; H, 6.64; N, 19.54.

URBANA, ILL.

(15) Audrieth, Gher, and Smith, *J. Org. Chem.*, 20, 1288 (1955).

(16) The melting point of 193° was observed on slow heating. However, this compound, like (VII), will melt on rapid immersion at temperatures as much as 15° below this value.

[CONTRIBUTION FROM THE MORLEY CHEMISTRY LABORATORY, WESTERN RESERVE UNIVERSITY]

Use of Sodium Hydride in Alkylation of Urethans

RALPH L. DANNLEY AND MARVIN LUKIN[1]

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By the use of sodium hydride, representative urethans have been alkylated with benzyl and primary alkyl halides in yields of 68–96%. The best results were obtained using excess alkyl halide or dimethylformamide as solvents. Secondary alkyl groups could not be introduced by the procedure. Although the alkylation of an *N*-perfluoroalkyl urethan (ethyl *N*-perfluoropropylcarbamate) was unsuccessful, an unusual hydrolysis product (ethyl *N*-perfluoropropionylcarbamate) was isolated.

The alkylation of urethans has received little attention since a compound which might be synthesized by this method can generally be prepared more readily from the appropriate secondary amine and a chloroformate. Such alkylations might be of use in the synthesis of novel urethans, however, for it is possible to obtain carbamates (*e.g.*, the N-perfluoroalkyl type) corresponding to primary amines which have never been isolated.

It was therefore decided to develop a general procedure for the alkylation of urethans. Kraft[2] had reported that treatment of ethyl carbamate with metallic sodium produced a salt which reacted with methyl iodide to give ethyl N-methylcarbamate. In developing a general procedure, however, sodium hydride appeared to be a more promising reagent than sodium for the step of salt formation. Sodium hydride has been used very successfully in the alkylation of simple amides[3] and has the advantage that it does not react with alkyl halides.[4]

The present work was undertaken with several objectives: first, to find whether sodium hydride could be used successfully in the alkylation of urethans; second, to select the solvents most desirable for use as diluents for the reaction mixtures; third, to determine yields from the reactions of typical alkylating reagents with representative urethans; and fourth, to attempt the alkyation of an N-perfluoroalkylurethan.

EXPERIMENTAL

Reagents. Sodium hydride (Metal Hydrides) and Eastman Kodak White-Label grades of ethyl N-methylcarbamate, *n*-butyl bromide, methyl iodide and benzyl chloride were used without purification. Allyl chloride was redistilled before use. Toluene and xylene were dried over sodium wire and dimethylformamide (Rohm & Haas) was dried with Drierite. The N-phenylurethan and N-benzylurethan were prepared from the respective amines and ethyl chlorocarbonate as described in a previous paper.[5]

Butylation of ethyl N-methylcarbamate. To a mixture of 72.1 g. (0.7 mole) of ethyl N-methylcarbamate and 191.8 g. (1.4 moles) of *n*-butyl bromide was added 19.2 g. (0.8 mole) of sodium hydride. The exothermic reaction caused the temperature to rise and the mixture refluxed spontaneously for about 0.5 hr. After stirring and refluxing for an additional 10 hr., the sodium bromide was removed by filtration. The salt cake was washed with two 100-ml. portions of ether and the ether washings were added to the filtrate. After removal of the ether and excess butyl bromide from the filtrate at atmospheric pressure, the residue was distilled *in vacuo* through a Todd column to give 91 g. (82% yield) of N-methyl-N-*n*-butylurethan (b.p. 91° at 20 mm.; n_D^{20} 1.4255; d_{25}^{25} 0.9159).

Anal. Calcd. for $C_8H_{17}NO_2$: C, 60.33; H, 10.78. Found: C, 60.77; H, 11.00.

Additional alkylations of N-methylurethan with butyl bromide were performed in various solvents as shown in Table I. In each instance the procedure was essentially identical with the experiment already described.

Benzylation of ethyl N-methylcarbamate. When a mixture of 72.1 g. (0.7 mole) of ethyl N-methylcarbamate, 177.1 g. (1.4 moles) of benzyl chloride and 19.2 g. (0.8 mole) of sodium hydride was stirred at room temperature, a very slow evolution of hydrogen occurred. Upon heating, the reaction became exothermic and benzyl chloride refluxed. The mixture was allowed to cool to 120° and maintained at this temperature for 18 hr. After addition of 10 ml. of ethanol to decompose the excess sodium hydride, 200 ml. of water were added and the aqueous layer separated and washed with three 75-ml. portions of ether. The combined organic layer and ether washings were dried over Drierite and distilled through a glass helices-packed column to yield 83.0 g. (61%) of ethyl N-methyl-N-benzylcarbamate, b.p. 100–101° (2.5 mm.), n_D^{20} 1.5052, d_{25}^{25} 1.049.

Anal. Calcd. for $C_{11}H_{15}NO_2$: C, 68.36; H, 7.84. Found: C, 68.14; H, 7.64.

Benzylation of ethyl N-phenylcarbamate. From a mixture of 33 g. of ethyl carbanilate, 5.28 g. of sodium hydride and 31.6 g. of benzyl chloride in 200 ml. of xylene kept at reflux for 24 hr. was obtained 51.0 g. (75% yield) of ethyl N-benzylcarbanilate, b.p. 135–136° (2.5 mm.), n_D^{20} 1.5677, d_{25}^{25} 1.099 (lit.[6] d_4^{35} 1.076). The procedure for isolation of the product was identical with that used in the preparation of ethyl N-methyl-N-benzylcarbamate.

Allylation of ethyl N-phenylcarbamate. The reaction of 82.5 g. of N-phenylurethan, 76.5 g. of allyl chloride, and 12.65 g. of sodium hydride in 150 ml. of dimethylformamide was quite vigorous. After the initial reaction subsided, the mixture was heated at gentle reflux for 6 hr. After decomposing the excess sodium hydride with 10 ml. of ethanol, 180 ml. of chloroform was added and the mixture was poured into 700 ml. of water. The aqueous layer was separated and extracted with additional chloroform. The combined chloroform solutions were dried over Drierite and distilled *in vacuo* to yield a fraction boiling from 98–102°

(1) From the thesis submitted by Marvin Lukin to the Graduate School of Western Reserve University in partial fulfillment of the requirements for the doctor's degree.

(2) F. Kraft, *Ber.*, **23**, 2785 (1890).

(3) W. Fones, *J. Org. Chem.*, **14**, 1099 (1949).

(4) S. Cristol, J. Ragsdale, and J. Meek, *J. Am. Chem. Soc.*, **71**, 1863 (1949).

(5) R. L. Dannley, M. Lukin, and J. Shapiro, *J. Org. Chem.*, **20**, 92 (1955).

(6) McBain, Harvey, and Smith, *J. Phys. Chem.*, **30**, 314 (1926).

TABLE I

REAGENTS AND PRODUCTS OF ALKYLATIONS PER MOLE OF STARTING ETHYL CARBAMATE

Starting Urethan	Alkylating Halide	Halide, Moles	NaH, Moles	Solvent	Solvent, Moles	Product Urethan, Moles
N-methyl	n-C_4H_9Br	2.00	1.14	None	—	0.82
N-methyl	n-C_4H_9Br[a]	1.50	1.00	Xylene	1.17	.43
N-methyl	n-C_4H_9Br[b]	1.50	1.07	Dimethylformamide	2.78	.60
N-methyl	n-C_4H_9Br[c]	0.97	0.97	$CHCl_3$	1.84	.10
N-methyl	$C_6H_5CH_2Cl$	2.00	1.14	None	—	.61
N-methyl	$C_6H_5CH_2Cl$[d]	1.55	1.17	Toluene	5.82	.54
N-methyl	$C_6H_5CH_2Cl$[e]	1.50	1.17	Dimethylformamide	1.82	.68
N-phenyl	$C_6H_5CH_2Cl$	1.25	1.10	Xylene	8.20	.75
N-phenyl	$C_6H_5CH_2Cl$[f]	1.25	1.10	Dimethylformamide	1.37	.66
N-phenyl	$CH_2{=}C(H){-}CH_2Cl$	2.00	1.10	Dimethylformamide	3.89	.93
N-benzyl	CH_3I[g]	2.00	1.10	Dimethylformamide	1.56	.79

[a] Refluxed 15 hr. [b] Temperature maintained at 60° for 12 hr. [c] Much sodium hydride left unreacted even though the mixture was refluxed for 18 hr. [d] Benzyl chloride added to a stirred mixture of sodium hydride and the urethan in toluene. The mixture was then refluxed for 30 hr. [e] Temperature maintained at 100° for 18 hr. [f] Temperature of 85° maintained for 18 hr. and chloroform used to extract the product. [g] Refluxed for 5 hr.

at 1.5 mm. To insure the absence of unalkylated urethan in the product, a benzene solution of the fraction was refluxed with 5 g. of sodium hydride for 3 hr. and then filtered. Distillation of the filtrate through a helices-packed column gave 95 g. (93% yield) of ethyl N-allyl-N-phenylcarbamate, b.p. 115–116° (4.5 mm.), n_D^{20} 1.5159; d_{25}^{25} 1.046.

Anal. Calcd. for $C_{12}H_{15}NO_2$: C, 70.21; H, 7.38. Found: C, 70.23; H, 7.28.

Attempted alkylation of urethans with secondary halides. In the two experiments tried (the s-butylation of ethyl N-methylcarbamate and the isopropylation of N-phenyl urethan) olefins were formed by dehydrohalogenation of the halides and the starting urethans were recovered unchanged.

Attempted alkylation of ethyl N-perfluoropropylcarbamate. Although the desired alkylation was not obtained, an unusual hydrolysis of the urethan was observed. Ten grams (0.039 mole) of N-perfluoropropylurethan[7] were added dropwise to a suspension of 0.98 g. (0.041 mole) of sodium hydride in 16.03 g. (0.117 mole) of butyl bromide. The reaction mixture was maintained at room temperature for 18 hr. and then refluxed for a day. The excess hydride was decomposed with wet ether and 10 ml. of water added. The organic layer was separated and the aqueous layer extracted with ether. The combined ethereal solutions were dried over Drierite and distilled to give 1.45 g. (16% yield) of ethyl N-perfluoropropionylcarbamate (m.p. 60–61°).

Anal. Calcd. for $C_6H_6F_5NO_3$: C, 30.65; H, 2.58; F, 40.40. Found: C, 30.66; H, 2.68; F, 39.5.

The identity of this product was proved through alcoholysis of an 0.5-gram sample in 4 ml. of refluxing anhydrous ethanol. Two ml. of this solution were distilled and the residue evaporated and distilled *in vacuo* to give 35 mg. (b.p. 73° at 12 mm.) of ethyl carbamate. After recrystallization from ligroin the urethan melted at 49–50° and addition of an authentic sample of ethyl carbamate did not depress the melting point.

The 2-ml. distillate was dissolved in anhydrous ether and the ether solution saturated with anhydrous ammonia. Evaporation of the solvent left 117 mg. of perfluoropropionamide, m.p. 95–96° (lit.[8] m.p. 95–95.5°).

The ethyl N-perfluoropropionylcarbamate undoubtedly was formed by hydrolysis of unchanged urethan while working up the reaction mixture.

Other methods of alkylation of this urethan were attempted without success. Use of dimethylformamide as a solvent, substitution of methyl iodide for the butyl bromide, and replacement of the sodium hydride with silver oxide all produced oils of high boiling point and low fluorine content.

DISCUSSION

The alkylation of urethans through the use of sodium hydride generally proceeded in good yield using an excess of the alkylating halide as a reaction medium. The use of excess halide, however, may sometimes be undesirable either due to the cost or unavailability of the reagent. Of several diluents tried, dimethylformamide generally gave rise to the best yields. The advantage in yield is not as remarkable as that observed by Sheehan and Bolhofer[9] in the use of dimethylformamide in the analogous Gabriel synthesis, but may again be related to its solvent properties for the salts formed as intermediates in the reaction.

The use of secondary halides led to olefin formation and recovery of the original urethan. Since alkyl halides do not react with sodium hydride, the dehydrohalogenation must result from reaction with the sodium derivative of the urethan. In contrast, Fones[3] did succeed in alkylating acetanilide in 53% yield with isopropyl bromide using sodium hydride as the condensing agent. The success of Fones may be due to the lower basicity of the salt of the simple anilide as compared to the salt of the urethan.

The alkylation of the N-perfluoroalkyl urethans was unsuccessful despite a variety of modifications of the general procedure. The inability to alkylate

(7) A. Albrecht, D. Husted, U. S. Patent 2,617,817; *Chem. Abstr.*, 47, 8774 (1953).

(8) R. Haszeldine and K. Leedham, *J. Chem. Soc.* 1548, (1953).

(9) J. Sheehan and W. Bolhofer, *J. Am. Chem. Soc.*, 72, 2786 (1950).

may be attributed to predominant competitive reactions of the fluorine atoms alpha to the nitrogen. The great reactivity of such fluorine atoms has been previously reported.[10]

Acknowledgment. We are indebted to the Research Corporation for financial aid in support of this work.

CLEVELAND, OHIO

(10) (*a*) D. Barr and R. Haszeldine, *J. Chem. Soc.*, 2532 (1955); (*b*) R. L. Dannley and M. Lukin, *J. Org. Chem.*, 21,1036 (1956); (c) R. L. Dannley, R. G. Taborsky, and M. Lukin, *J. Org. Chem.*, **21**, 1318 (1956).

[CONTRIBUTION NO. 998 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

Pyridylethylation of Active Hydrogen Compounds. VI. Reactions of Ketones, Alkylpyridines, and Alkylquinolines with 2- and 4-Vinylpyridine[1,2,3]

GEORGE MAGNUS AND ROBERT LEVINE

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A study has been made of the conjugate addition reactions of a series of ketones with 4-vinylpyridine and of four alkylpyridines and two alkylquinolines with 2- and 4-vinylpyridine.

In 1947 Doering and Weil published a classical paper[4] in which they demonstrated elegantly that 2- and 4-vinylpyridine undergo conjugate addition reactions with a representative group of nucleophilic reagents. We have extended their observations and in previous papers from this laboratory the reactions of 2-vinylpyridine with ketones[5,6] and of both 2- and 4-vinylpyridine with ammonia,[2] amines,[2,7,8] amides,[2] and nitriles[2] were discussed.

The present paper is concerned with the reactions of 4-vinylpyridine with a series of ketones and of both 2- and 4-vinylpyridine with several alkylated tar bases. Apparently the only previously reported direct pyridylethylation of a ketone with 4-vinylpyridine appears in a paper by Levine and Wilt,[5] who obtained a 21.5% yield of phenyl γ-(4-pyridyl)-propyl ketone by the interaction of a 2:1:0.2 molar ratio of acetophenone, 4-vinylpyridine and sodium for a reaction time of 4 hr. This compound also has been prepared indirectly by the ketonic cleavage of ethyl α-[β-(4-pyridyl)ethyl]benzoylacetate,[9] which was obtained by the reaction of 4-vinylpyridine with ethyl benzoylacetate.

In the present study the reaction between acetophenone, 4-vinylpyridine and sodium has been reinvestigated. The interaction of a 2:1 molar ratio of ketone to 4-vinylpyridine for periods of 2, 4, and 6 hr. (Table I) gave mixtures of the monopyridylethylated product, phenyl γ-(4-pyridyl)-propyl ketone (16 to 18%) and the dipyridylethylated product, 3-benzoyl-1,5-di-(4-pyridyl)pentane, (65 to 73%). Even when a molar ratio of ketone to vinylpyridine of 4:1 was used in an attempt to greatly increase the amount of mono- and decrease the dipyridylethylated product, these derivatives were obtained in 21.6% and 36% yields, respectively. These results appear to indicate that 4-vinylpyridine reacts more readily with the initially formed monopyridylethylated compound to give the dipyridylethylated derivative than it does with acetophenone to give the monopyridylethylated compound.

The reaction of a 2:1 molar ratio of *p*-methylacetophenone to 4-vinylpyridine gave a low yield of the mono- (18.2%) and a higher yield of the dipyridylethylated (46.8%) product. Although under similar conditions the reaction of propiophenone with 4-vinylpyridine gave a high yield (88.5%) of the monopyridylethylated product, when this reaction was repeated using a 1:2 ratio of ketone to 4-vinylpyridine, essentially equal amounts of the mono- (43.4%) and the dipyridylethylated (41.0%) products were obtained.

Five symmetrical ketones have been condensed with 4-vinylpyridine (Table I). It may be seen that with the exception of acetone, each of these ketones was monopyridylethylated in fair to good yield. In the cyclohexanone reaction a mixture of a considerable amount of self-condensed ketone, 2-(1-cyclohexenyl)cyclohexanone, 40.8% of the mono-

(1) This paper is based on part of a thesis presented by George Magnus to the graduate faculty of the University of Pittsburgh in partial fulfillment of the requirements of the Ph.D. degree.

(2) For the previous paper in this series, see G. Magnus and R. Levine, *J. Am. Chem. Soc.*, **78**, 4127 (1956).

(3) This work was performed under Contract No. AT(301)-670 between the U. S. Atomic Energy Commission and the University of Pittsburgh.

(4) W. von E. Doering and R. A. N. Weil, *J. Am. Chem. Soc.*, **69**, 2461 (1947).

(5) R. Levine and M. H. Wilt, *J. Am. Chem. Soc.*, **74**, 342 (1952).

(6) M. H. Wilt and R. Levine, *J. Am. Chem. Soc.*, **75**, 1368 (1953).

(7) H. E. Reich and R. Levine, *J. Am. Chem. Soc.*, **77**, 4913 (1955).

(8) H. E. Reich and R. Levine, *J. Am. Chem. Soc.*, **77**, 5434 (1955).

(9) V. Boekelheide and J. H. Mason, *J. Am. Chem. Soc.*, **73**, 2356 (1951).

TABLE I

REACTIONS OF 4-VINYLPYRIDINE WITH KETONES

Ketone	Yield, %	B.p., °C.	Mm.	Products Formula	% Nitrogen Calcd.	Found	Monopicrates Formula	% Nitrogen Calcd.	Found	M.p., °C.
Acetophenone[a,b]	18.4	78–79 (m.p.)[c]								
	66.0[d]	232–235	1	$C_{22}H_{22}NO$	8.48	8.16	$C_{34}H_{28}N_8O_{15}$[e,f]	14.21	13.88	172.8–173.8
p-Methylaceto-phenone[a]	18.2	72–73 (m.p.)		$C_{16}H_{17}NO$	5.86	6.06	$C_{22}H_{20}N_4O_8$	11.96	12.12	127–128
	46.8[d]	247–250	1	$C_{23}H_{24}N_2O$	[g]		$C_{35}H_{30}N_8O_{15}$[e]	[h]		173.5–174.5
Propiophenone	88.5[a]	198–200	4	$C_{16}H_{17}NO$	5.86	5.98	$C_{22}H_{20}N_4O_8$	11.96	11.84	137–138
	43.4[i]	198–200	4							
	41.0[d,i]	245–247	1.5	$C_{23}H_{24}N_2O$	8.13	8.16	$C_{35}H_{30}N_8O_{15}$[e]	13.96	13.55	191–192
Cyclohexanone[a]	40.8	157–160	1.5	$C_{13}H_{17}NO$	6.89	7.33	$C_{19}H_{20}N_4O_8$	12.95	12.67	129.5–131
	36.4[d,j]	245–255	2	$C_{20}H_{24}N_2O$	[k]		$C_{32}H_{30}N_8O_{15}$[e]	[l]		199–200
Acetone[a]	5.0	109–111	2	$C_{10}H_{13}NO$	8.59	8.93	$C_{16}H_{16}N_4O_8$	14.29	14.17	113–114
Diethyl[a]	45.0	125–128	1.5	$C_{12}H_{17}NO$	7.32	7.57	$C_{18}H_{20}N_4O_8$	13.33	13.27	102–103
Diisopropyl[a]	64.0[m]	125–127	1	$C_{14}H_{21}NO$	6.39	6.93	$C_{20}H_{24}N_4O_8$	12.50	12.81	110.2–111.2
Diisobutyl[a]	48.6	147–150	1.5	$C_{16}H_{25}NO$	5.66	5.48	$C_{22}H_{28}N_4O_8$	11.76	11.65	113.5–114.5
Methyl ethyl[a]	26.0	136–138	4	$C_{11}H_{15}NO$	7.91	8.18	$C_{17}H_{18}N_4O_8$	13.78	13.76	109–110
Methyl isopropyl[a]	64.0	121–124	1.5	$C_{12}H_{17}NO$	7.32	7.67	$C_{18}H_{20}N_4O_8$	13.33	13.05	125.5–126.5
Methyl benzyl	7.5[a]	194–195	5.0	$C_{16}H_{17}NO$	[n]		$C_{22}H_{20}N_4O_8$	11.96	11.54	133.5–134.5
	79.5[o]	194–195	5.0							

[a] Molar ratio of ketone:4-vinylpyridine:sodium was 2:1:0.2 and reaction time was 2 hr. [b] Reaction time of 4 hr. gave 17.6% of mono- and 73.0% of dipyridylethylated product and a 6-hr. reaction time gave 16.4% mono and 65.3% di. Reaction of a 1:0.25:0.05 molar ratio of ketone:4-vinylpyridine:sodium gave 21.6% mono and 36% di. [c] See refs. 5 and 9; b.p. 190–195° at 1.5 mm. [d] This is a dipyridylethylated product. All the products not so marked are monopyridylethylated ketones. [e] This is a dipicrate. [f] *Anal.* Calcd.: C, 51.77; H, 3.57. Found: C, 51.96; H, 3.43. [g] *Anal.* Calcd.: C, 80.23; H, 6.97. Found: C, 80.31; H, 6.63. [h] *Anal.* Calcd.: C, 52.36; H, 3.74. Found: C, 52.54; H, 3.50. [i] The molar ratio of ketone:4-vinylpyridine:sodium was 1:2:0.2 and the reaction time was 2 hr. [j] There was also obtained 23.5 g. of 2-(1-cyclohexenyl)cyclohexanone (b.p. 136–138° at 10 mm.; semicarbazone, m.p. 175–177° [J. Reese, *Ber.*, **75B**, 384 (1942)]. [k] *Anal.* Calcd.: C, 77.92; H, 7.79. Found: C, 77.48; H, 7.70. [l] *Anal.* Calcd.: C, 50.13; H, 3.91. Found: C, 49.86; H, 3.77. [m] There was obtained 3.5 g. (6.6%) of 1,4-di-(4-pyridyl)butane, m.p. 117.5–118.5° (see refs. 2 and 17). [n] *Anal.* Calcd.: C, 80.33; H, 7.11. Found: C, 79.90; H, 6.99. [o] A mixture of 5 ml. of Triton B and 0.5 mole each of ketone and 4-vinylpyridine was kept at 70–75° for 2 hr. and then processed.

pyridylethylated product, and 36.4% of the dipyridylethylated product were isolated. Although the structure of the last compound was not elucidated, it is suggested that it is 2,2-bis-[2-(4-pyridyl)-ethyl]cyclohexanone by analogy with the reaction of cyclohexanone with acrylonitrile, which apparently gives 2,2-bis-(β-cyanoethyl)cyclohexanone.[10] As a by-product in the reaction of diisopropyl ketone with 4-vinylpyridine, there was obtained a small amount (6.6%) of the bimolecular reduction product of 4-vinylpyridine, 1,4-di(4-pyridyl)butane. This compound was previously obtained in the reaction between acetamide and 4-vinylpyridine.[2]

Although acetone has been pyridylethylated by 4-vinylpyridine to give only extremely low yields (4 to 5%) of 5-(4-pyridyl)-2-pentanone, this ketone was prepared in an over-all yield of 56% by condensing 4-vinylpyridine with ethyl acetoacetate to give ethyl α-[β-(4-pyridyl)ethyl]acetoacetate (67%), which was then cleaved to the desired ketone in 84% yield by refluxing with concentrated hydrochloric acid.

While the structures of the first eight products listed in Table I are unambiguous, it is entirely possible that the reactions of 4-vinylpyridine with the unsymmetrical ketones, methyl ethyl, methyl isopropyl and methyl benzyl ketones, could give rise to isomeric condensation products by pyridylethylation at either or both of the α-carbon atoms of these ketones. It was definitely established that the product derived from methyl ethyl ketone and 4-vinylpyridine is 3-methyl-5-(4-pyridyl)-2-pentanone, II, *i.e.*, condensation had occurred at the methylene carbon atom of the ketone. This was done by showing that the product was identical with an authentic sample of II, which was prepared by treating ethyl α-methylacetoacetate with 4-vinylpyridine to give ethyl α-methyl,α-[β-(4-pyridyl)-ethyl]acetoacetate, III, which was then subjected to ketonic cleavage.

$$CH_3COCH_2CH_3 + 4\text{-}C_5H_4NCH{=}CH_2 \xrightarrow{Na}$$
I

$$CH_3COCH(CH_3)CH_2CH_2C_5H_4N\text{-}(4)$$
II

$$CH_3COCH(CH_3)CO_2C_2H_5 + I \xrightarrow{Na}$$
$$CH_3COC(CH_3)(CO_2C_2H_5)CH_2CH_2C_5H_4N\text{-}(4)$$
III

$$III \xrightarrow{HCl/H_2O} II$$

It was also shown that the compound derived from methyl isopropyl ketone and 4-vinylpyridine is 3,3-dimethyl-5-(4-pyridyl)-2-pentanone (*i.e.*, reaction had occurred at the methinyl carbon atom of the ketone) by subjecting the product to the haloform reaction and obtaining 2,2-dimethyl-4-(4-

(10) H. A. Bruson and T. W. Riener, *J. Am. Chem. Soc.*, 64, 2850 (1942).

pyridyl)butanoic acid. An authentic sample of this acid was prepared by saponifying ethyl 2,2-dimethyl-4-(4-pyridyl)butanoate, which was synthesized in 28.5% yield by condensing 4-vinylpyridine with ethyl isobutyrate. There is also little doubt that the compound derived from methyl benzyl ketone is 3-phenyl-5-(4-pyridyl)-2-pentanone since it also undergoes a haloform reaction.

It is well known that the hydrogen atoms of the methyl groups in 2- and 4-picoline are quite acidic. The reactivity of these compounds has often been compared with that of methyl ketones and therefore it is not surprising that they may be effectively alkylated[11,12] and acylated[13-15] at their side chains. It was therefore of interest to determine whether these and related compounds could be condensed with 2- and 4-vinylpyridine. The results obtained are listed in Table II. Prior to our study, Leonard and Boyer[16] had condensed 2-vinylpyridine with 2-picoline using sodium as the condensing agent and obtained a 33% yield of 1,3-di-(2-pyridyl)propane. In the present study this reaction was repeated and a 37% yield of the same product was obtained. Jampolsky *et al.*[17] have studied the reaction between 4-vinylpyridine and 4-picoline and claim that while sodium was an ineffective catalyst for this condensation, the use of potassium gave a 41% yield of 1,3-di(4-pyridyl)-propane. Contrary to these findings we have been able to use sodium successfully and have obtained a 41% yield of the expected product. We have also prepared the mixed dipyridylpropane, 1-(2-pyridyl)-3-(4-pyridyl)propane by the reaction of 2-picoline with 4-vinylpyridine and 4-picoline with 2-vinylpyridine. It is interesting to note that the former route gave a 28% yield and the latter route a 10% yield of product. It has also been possible to pyridylethylate 2- and 4-ethylpyridine with both 2- and 4-vinylpyridine in fair to good yields. However, both 4-*n*-propyl- and 4-isopropylpyridine failed to condense with 4-vinylpyridine. In the quinoline series, although quinaldine and lepidine have been pyridylethylated with 2-vinylpyridine in low yield, both of these tar bases failed to condense with 4-vinylpyridine.

TABLE II

REACTIONS OF 2- AND 4-VINYLPYRIDINE WITH TAR BASES

Tar Base	Vinylpyridine	Yield, %	Products B.P. °C.	Mm.	Formula	% Nitrogen Calcd.	Found	Derivative Formula	% Nitrogen Calcd.	Found	M.P., °C.
2-Picoline[a]	2	37.4	*130–135*	1.5							208–209[b,c]
	4	28.2	128–130	1.0	$C_{13}H_{14}N_2$	14.14	14.51	$C_{25}H_{20}N_8O_{16}$[d]	16.27	16.57	211–212
4-Picoline	2	10.1	140–142	2.0		14.14	14.45	$C_{25}H_{20}N_8O_{14}$[b]	17.04	16.76	178.5–179.5
	4	40.6	158–162	2.0		14.14	13.77	[b]	17.04	17.20	185–186
			62–65 (m.p.)[e]								
2-Ethylpyridine	2	62.5	*134–136*	2.0	$C_{14}H_{16}N_2$	13.21	12.84	$C_{26}H_{22}N_8O_{16}$[d]	15.95	15.92	175.5–176.5
	4	34.4	160–162	6.0		13.21	12.99	[d]	15.95	16.25	188–189
4-Ethylpyridine	2	37.4	140–142	1.5		13.21	13.56	[d]	15.95	16.20	185.5–186.0
	4	50.8	160–161	2.0		13.21	12.96	[d]	15.95	15.81	192–192.5
Quinaldine	2	21.0	182–184	1.0	$C_{17}H_{16}N_2$	11.29	11.45	$C_{29}H_{22}N_8O_{14}$[b]	15.87	16.28	210–211
	4	*0.0*									
Lepidine	2	17.0	185–187	1.0	$C_{17}H_{16}N_2$	11.29	11.35	$C_{29}H_{22}N_8O_{14}$[b]	15.87	16.13	214–215
	4	0.0									

[a] In all reactions a 2:1:0.1 molar ratio of tar base:vinylpyridine:sodium and a 2-hr. reaction time were employed. [b] This derivative is a dipicrate. [c] See ref. 16. [d] This derivative is a distyphnate. [e] A melting point of 57–60° is reported in ref. 17.

EXPERIMENTAL[18]

General procedure for reactions of ketones with 4-vinylpyridine using sodium as the catalyst and acetophenone as an example. Acetophenone (120.0 g., 1.0 mole), 4-vinylpyridine (52.5 g., 0.50 mole), and 2.3 g. (0.10 mole) of sodium were placed in the previously described reactor.[5] After stirring the mixture for a few minutes, a sufficiently vigorous exothermic reaction occurred so that the mixture refluxed. After about 15 min., the exothermic reaction began to subside. Heat was then applied and the mixture was refluxed for an additional 2 hr. After cooling to room temperature the contents of the flask was poured onto a mixture of ice and 100 ml. of concentrated hydrochloric acid, and the aqueous solution was extracted with three 100-ml. portions of chloroform. The combined chloroform extracts (Extract I) were dried over anhydrous sodium sulfate. The aqueous phase was made strongly basic by the addition of saturated

(11) For leading references, see "The Chemistry of the Alkali Amides. III," R. Levine and W. C. Fernelius, *Chem. Revs.*, **54**, 540 (1954).

(12) C. Osuch and R. Levine, *J. Am. Chem. Soc.*, **78**, 1723 (1956).

(13) N. N. Goldberg, L. B. Barkley, and R. Levine, *J. Am. Chem. Soc.*, **73**, 4301 (1951).

(14) N. N. Goldberg and R. Levine, *J. Am. Chem. Soc.*, **74**, 5217 (1952).

(15) N. N. Goldberg and R. Levine, *J. Am. Chem. Soc.*, **77**, 3647 (1955).

(16) N. J. Leonard and J. H. Boyer, *J. Am. Chem. Soc.*, **72**, 4818 (1950).

(17) L. M. Jampolsky, M. Baum, S. Kaiser, L. H. Sternbach, and M. W. Goldberg, *J. Am. Chem. Soc.*, **74**, 5222 (1952).

(18) The 2- and 4-vinylpyridine, 2- and 4-picoline, quinaldine and lepidine were kindly supplied by Dr. F. E. Cislak, Reilly Tar and Chemical Corp.

aqueous sodium carbonate solution, extracted with chloroform and dried over anhydrous sodium sulfate (Extract II). The solvents from Extracts I and II were removed by atmospheric distillation and the residues were distilled in vacuum. From Extract I there was obtained 20.0 g. of recovered acetophenone, b.p. 114–116° at 52 mm. and 20.0 g. neutral material, b.p. 190–225° at 0.5 mm. (probably self-condensation products of acetophenone). Extract II yielded 20.5 g. (18.4%) of phenyl γ-(4-pyridyl)propyl ketone b.p. 190–195° at 1.5 mm., m.p. 78–79°; 55.6 g. (66.0%) of 3-benzoyl-1,5-di-(4-pyridyl)pentane (b.p. 232–235° at 1 mm.) and 12.0 of a tarry, nitrogenous residue.

When Triton B was employed as the catalyst, the exothermic reaction mixtures were not allowed to reflux but were maintained at 70–75° by using an ice water bath when necessary.

Preparation of an authentic sample of 5-(4-pyridyl)-2-pentanone. A mixture of 52.0 g. (0.4 mole) of ethyl acetoacetate, 21.0 g. (0.2 mole) of 4-vinylpyridine and 0.6 g. (0.026 mole) of sodium was refluxed for 6 hr. and processed to give 31.5 g. (67.0%) of ethyl α-[β-(-4-pyridyl)-ethyl]-acetoacetate, b.p. 162–164° at 2.0 mm. This product, 90 ml. of concentrated hydrochloric acid, and 90 ml. of water were refluxed for 4 hr. and processed to give 18.3 g. (84%) of 5-(4-pyridyl)-2-pentanone, b.p. 102–105° at 1.0 mm. This compound formed a yellow picrate, m.p. 113–114° alone and when mixed with a sample prepared from the material obtained by the direct reaction of acetone with 4-vinylpyridine.

Preparation of authentic sample of 3-methyl-5-(4-pyridyl)-2-pentanone. A mixture of 72.0 g. (0.5 mole) of ethyl α-methylacetoacetate, 63.2 g. (0.6 mole) of 4-vinylpyridine and 2.0 g. (0.085 mole) of sodium was refluxed for 24 hr. and processed to give 37.0 g. (29.7%) of ethyl α-methyl-α-[β-(4-pyridyl)ethyl]acetoacetate, b.p. 154–157° at 1.5 mm. This product, 100 ml. of concentrated hydrochloric acid, and 100 ml. of water were refluxed for 16 hr. and processed to give 19.0 g. (61.7%) of 3-methyl-5-(4-pyridyl)-2-pentanone, b.p. 120–122° at 2 mm. This compound formed a yellow picrate, m.p. 109–110° alone and when mixed with a sample prepared from the material obtained by the direct reaction of methyl ethyl ketone with 4-vinylpyridine.

Proof of structure of adduct obtained from methyl isopropyl ketone and 4-vinylpyridine. (*a*) *Oxidation with potassium hypochlorite.* The adduct from methyl isopropyl ketone and 4-vinylpyridine (21.0 g., 0.11 mole) was oxidized with potassium hypochlorite using the procedure described previously[6] for the oxidation of 3,3-dimethyl-5-(2-pyridyl)-2-pentanone to give 2.5 g. (11.8%) of 2,2-dimethyl-4-(4-pyridyl)butanoic acid, m.p. 149.5–150.5° (from 95% ethanol).

Anal. Calcd. for $C_{11}H_{15}NO_2$: N, 7.25. Found: N, 7.48.

(*b*) *Preparation of an authentic sample of 2,2-dimethyl-4-(4-pyridyl)butanoic acid.* A mixture of 57.5 g. (0.50 mole) of ethyl isobutyrate, 52.6 g. (0.50 mole) of 4-vinylpyridine and 1.5 g. (0.065 mole) of sodium was refluxed for 3 hr. and processed to give 31.5 g. (28.5%) of ethyl 2,2-dimethyl-4-(4-pyridyl)butanoate, b.p. 118–120° at 1.5 mm. This ester formed a yellow picrate, m.p. 85.5–86.5° (from 95% ethanol).

Anal. Calcd. for $C_{19}H_{22}N_4O_9$: N, 12.44. Found: N, 12.61.

A mixture of 10.0 g. (0.05 mole) of the ester, 10.0 g. of sodium hydroxide and 100 ml. of water was refluxed until a homogeneous solution was obtained. The mixture was then cooled and acidified with glacial acetic acid to give 7.5 g. (77.5%) of 2,2-dimethyl-4-(4-pyridyl)butanoic acid, m.p. 149.5–150.5° alone and when mixed with a sample of the acid obtained in part (*a*).

General procedure for reactions of tar bases with 2- and 4-vinylpyridine using reaction between 2-ethylpyridine and 4-vinylpyridine as an example. A mixture of 2-ethylpyridine (52.5 g., 0.50 mole), 4-vinylpyridine (26.3 g., 0.25 mole) and 1.15 g. (0.05 mole) of sodium was placed in the reactor. Since no apparent reaction occurred, the mixture was heated cautiously to 96°. At this temperature a vigorous exothermic reaction took place and it was necessary to use an ice bath to control the reaction. After the exothermic reaction had subsided, the mixture was refluxed for 2 hr. and allowed to cool to room temperature. Absolute ethanol (5 ml.) was cautiously added and then the contents of the flask were poured onto a mixture of ice and water. The mixture was extracted with chloroform and processed in the regular manner to give 18.0 g. (34.4%) of 1-(4-pyridyl)-3-(2-pyridyl)butane, b.p. 160–162° at 6.0 mm. In addition, 34.0 g. of a mixture of recovered 2-ethylpyridine and 4-vinylpyridine, b.p. 60–62° at 35 mm., and 26.0 g. of a tarry nitrogenous residue were obtained.

PITTSBURGH 13, PA.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, OREGON STATE COLLEGE]

Pyrimidines VII: Cyclization of Ethyl Oxalate and Ethyl α-Oxalylpropionate with Urea and Certain of Its Analogs[1]

P. H. LAURSEN, W. A. THEWS, AND B. E. CHRISTENSEN

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Procedures have been established for the preparation of parabanic acid and thioparabanic acid by the condensation reactions of diethyl oxalate. Guanidine does not cyclize with diethyl oxalate but yields a linear product when reacted under the conditions cited above.

Guanidine and ethyl α-oxalylpropionate have been condensed in an alkaline medium to yield a noncyclic guanide. The guanide has been cyclized to an imidazoline derivative and that in turn enlarged to the pyrimidine-4-carboxylic acid.

The structure of the imidazoline derivative, and consequently the isomeric pyrimidine as well as the guanide, has been determined on the basis of: (1) the ease of hydrogenation of the olefinic unsaturation in ethyl-5(4)-[2-amino-4(5)-oxo-Δ^2-imidazolineidene]-2-propionate, (2) analytical data, and (3) the ultraviolet spectral data.

The condensation of urea with ethyl α-oxalylpropionate, in an acidic medium, yielded ethyl hydantoidene-2-propionate which was hydrolyzed to the acid and then rearranged to the isomeric pyrimidine-4-carboxylic acid. The analytical data and ultraviolet curves are given.

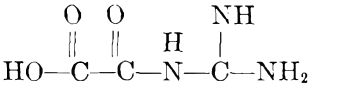
Condensations of the ester with formamidine and acetamidine were attempted yielding oils which were not characterized. Thiourea gave such a small amount of product that it did not seem feasible to continue work on that phase of the problem.

It is common knowledge that urea, thiourea, guanidine, and amidines condense readily with β-keto ester, β-diketones, cyanoacetates and malonates to yield linear condensation products or substituted pyrimidines. Numerous reactions of this type have been described in the more recent literature. Furthermore, the study of the condensation of these nitrogenous bases has also been extended to glyoxal and certain α-diketones.[2]

Condensations involving diethyl oxalate, on the other hand, have received scant attention, which is surprising in view of the importance of parabanic acid. Michael does mention its condensation with urea but reports no yields and fails to give detailed directions.[3]

In this laboratory, the reaction product of urea, diethyl oxalate, and sodium ethoxide was found to be an alcohol-insoluble salt which, when suspended in absolute alcohol and treated with sulfuric acid, yielded pure parabanic acid.

2-Thioparabanic acid was obtained by the corresponding sequence of reactions. However, the same experiment repeated with guanidine gave a linear product oxalylguanidine



as judged by (1) chemical analysis, (2) the fact that it reacted with ammonium hydroxide to yield a stable ammonium salt, and (3) it's failure to lose water when heated under 1-mm. pressure at 110° for 48 hr. Similar experiments in which acetamidine was substituted for urea gave a sodium salt which upon further treatment with sulfuric acid hydrolyzed to yield oxalic acid.

In case of intermediates in which the carbonyl is both alpha and beta to a carbethoxy such as exists in ethyl oxalacetate, there is a possibility of both ring systems being formed on cyclization. Some confusion as to the products of such cyclizations is to be noted in the earlier literature.[4] Apparently condensations under basic conditions yielded pyrimidine derivatives, while an acid medium gave a substituted hydantoin.

Recently, Mitchell, and Nyc[5] observed the cyclizations under acidic conditions which yielded hydantoins could rearrange, when treated with base, to yield pyrimidines. These workers hypothesized that the hydantoin opened to form an unsaturated hydantoic acid which was followed by ring closure to give a pyrimidine derivative. The validity of this hypothesis was confirmed by several supporting experiments.[6]

Condensations using diethyl α-oxalylpropionate were first reported by Johnson[7] who noted that the reaction product obtained from an alkaline medium using pseudomethylthiourea was either the salt or ester of 5-methyl-2-methylmercapto-6-oxopyrimidine-4-carboxylate depending on the amount of alkali employed; this compound was converted to thymine-4-carboxylic acid. Since the condensation was carried out in a basic medium it may be likely that the pyrimidine, in this instance, did not arise

(1) This work was supported in part by grants from the Division of Research Grants and Fellowships, National Institutes of Health, Public Health Service. Published with the approval of the Monographs Publications Committee, Oregon State College, as Research Paper No. 314 School of Science, Department of Chemistry.

(2) H. Pauly, and H. Sauter, *Ber.*, **63B**, 2063–9 (1930). H. Biltz and Rinspel, *Ber.*, **41**, 1379 (1908). A. P. N. Franchimont and E. A. Klobbie, *Rec. trav. chim.*, **7**, 236 (1888). I. Bengelsdorf, *J. Am. Chem. Soc.*, **75**, 3138–40 (1953).

(3) A. Michael, *J. prakt. Chem.*, **35**, 458 (1887).

(4) H. L. Wheeler, *Am. Chem. J.*, **38**, 358 (1907).

(5) H. K. Mitchell and J. F. Nyc, *J. Am. Chem. Soc.*, **69**, 674 (1947).

(6) H. K. Mitchell and J. F. Nyc, *J. Am. Chem. Soc.*, **69**, 1382 (1947).

(7) T. B. Johnson, *J. Biol. Chem.*, **3**, 299 (1907).

from a rearrangement of a hydantoin but by direct cyclization.

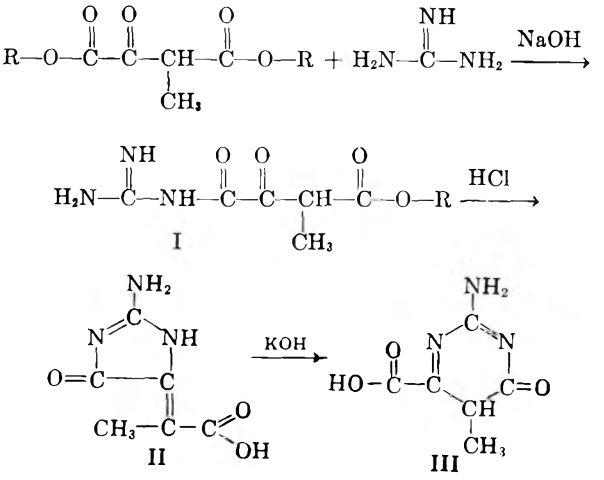
In 1949 Mentzer and Billet,[8] using Muller's[9] procedure, studied the condensation of diethyl α-oxalylpropionate with urea, which was reported to yield ethyl thymine-4-carboxylate. The saponification of the ester to the acid gave a product which was identical with the acid prepared by Johnson.[7] These workers, however, carried out their initial condensations in an acid medium in contrast to the basic conditions employed by Johnson. Although their acids were identical, the ester which Mentzer and Billet isolated was not the same as the one prepared by the esterification of thymine-4-carboxylic acid. On the basis of spectral studies and by making comparison to the 5-carbethoxymethylenehydantoin reported by Mitchell and Nyc,[6] these workers concluded that their initial condensation product was a hydantoin which, under the influence of alkali, opens and recyclizes to a pyrimidine.

The condensation of diethyl α-oxalylpropionate with amidines, guanidines or thiourea has received scant attention. Johnson[10] attempted the condensation with guanidine in aqueous media and reports a small yield which he did not characterize. In view of the interest which has since arisen in derivatives of orotic acid, as a result of the discovery of its presence in milk, it appeared worthwhile to investigate these reactions.

Initial experiments involving the condensation of amidines with diethyl α-oxalylpropionate resulted in an oily product which was not characterized. However the condensation in anhydrous methanolic medium with guanidine free base in absence of a condensing agent yielded an insoluble product which was found to be a noncyclic guanide (I) rather than the expected cyclic derivative. The treatment of this guanide with hydrochloric acid effected cyclization as judged by the solubility characteristics and melting point behavior of the product II. The ultraviolet spectrum of the compound II was similar to the hydantoin which had been described earlier by Mitchell and Nyc.[5] Furthermore, compound II was esterified and hydrogenated at low pressures with Adams catalyst. The relatively mild conditions of hydrogenation indicated olefinic unsaturation which would not have been possible if a six-membered ring had been formed in the cyclization. This observation not only confirmed the structure of the imadazoline but also fixed that of the guanide, compound I (see Fig. 1).

Since pyrimidines had been reported as cyclization products of like condensations carried out in the presence of inorganic bases, compound II was heated in the presence of aqueous potassium hydroxide. Acidification of the reaction mixture yielded an acid product, III, which had a considerably higher melting point. The ultraviolet absorption spectrum of III closely resembled that reported for orotic acid[5] (see Fig. 2). On this basis the pyrimidine structure was assigned to compound III.

Fig. 1



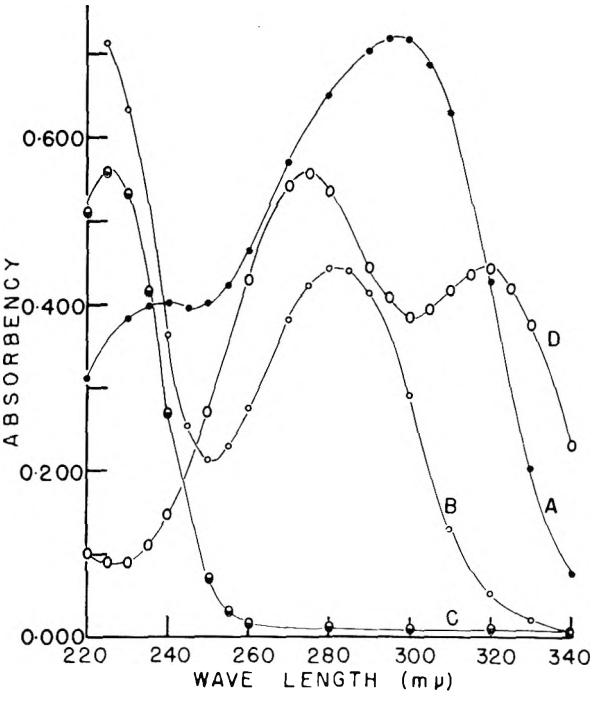


FIG. 2.—A = 5(4)-(2-AMINO-4(5)-OXO-Δ^2-IMIDAZOLINEIDENE)-2-PROPANOIC ACID (II). B = 2-AMINO-5-METHYL-6-OXO-PYRIMIDINE-4-CARBOXYLIC ACID (III). C = ETHYL-5(4)-(2-AMINO-4(5)-OXO-Δ^2-IMIDAZOLINE)-2-PROPIONATE. D = ETHYL-5(4)-(2-AMINO-4(5)-OXO-Δ-IMIDAZOLINEIDENE)-2-PROPIONATE

The condensation of urea with diethyl α-oxalylpropionate has been effected recently by Mentzer and Billet[8] who employed an acidic medium and used hydrogen chloride as the condensing agent. Their reaction product yielded an ester which was

(8) C. Mentzer and D. Billet, *Compt. rend.*, 288, 402 (1949).

(9) R. Muller, *J. prakt. Chem.*, 56, 475 (1897).

(10) T. B. Johnson, *Am. Chem., J.*, 49, 287 (1913).

saponified in basic medium and then acidified to yield a product to which they assigned the structure thymine-4-carboxylic acid.

Although these workers also identified their initial condensation product (the ester) as a hydantoin, no analytical data were given to support this conclusion.

This condensation has been confirmed in this laboratory, and the existence of a hydantoin intermediate has been established on the basis of analytical data and spectral data (see Fig. 3). Although the condensations with guanidine and urea gave similar products which rearranged to pyrimidine derivatives it is interesting to note that no noncyclic intermediate was observed in condensations involving urea. The tendency of guanidine to form noncyclic guanides under like conditions has been observed in other reactions.

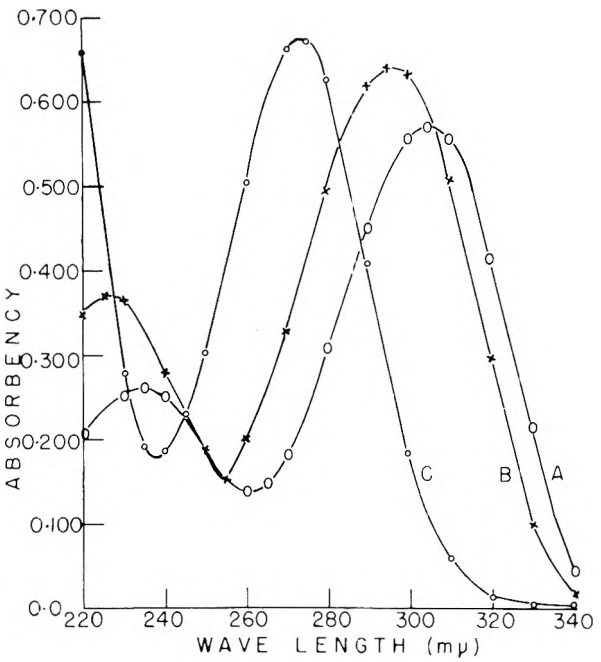


FIG. 3.—A = ETHYL (HYDANTOIDENE)-2-PROPIONATE. B = (HYDANTOIDENE)-2-PROPIONIC ACID. C = 2,6-DIOXO-5-METHYLPYRIMIDINE-4-CARBOXYLIC ACID.

Since condensations with thiourea and diethyl α-oxalylpropionate have not been run under the conditions here employed, this work was repeated with thiourea. Using sodium ethoxide as a condensing agent in ethanolic medium gave such a small yield of reaction product that it did not seem feasible to pursue the problem further. Condensations attempted using Muller's[9] procedure likewise failed to yield appreciable product.

EXPERIMENTAL

Parabanic acid. Into a 250-ml. three-necked flask equipped with reflux condenser and stirrer were placed, in this order, 100 ml. of absolute ethanol, 7.9 g. (0.34 mole) of sodium, and 10.3 g. (0.17 mole) of urea. As this stirred mixture was slowly brought to a reflux temperature 25 g. (0.17 mole) of diethyl oxalate was added dropwise; the mixture was then refluxed for 2 hr. and cooled. The product, a white sodio salt was filtered and dried. Yield, 29 g.

Anal. Calcd. for $C_3H_2N_2O_4Na_2$: Na, 25.7. Found: Na, 26.2.

The sodio salt was resuspended in absolute alcohol and 0.17 mole of concentrated sulfuric acid was added dropwise with stirring which was continued for several hours. After cooling, the insoluble sodium sulfate was removed and the alcohol then evaporated. This yielded a white crystalline product which was in turn recrystallized from a minimum quantity of hot water. Yield, 13.9 g. (72%); neut. equiv. 112; m.p. 247°.

Anal. Calcd. for $C_3H_2N_2O_3$: C, 31.59; H, 1.77. Found: C, 31.3; H, 1.93.

Thioparabanic acid. To 25 ml. of an anhydrous alcoholic solution containing 2 g. (0.09 mole) of sodium and 3.35 g. (0.044 mole) of thiourea were slowly added with stirring and heating 6.42 g. (0.044 mole) of diethyl oxalate. This mixture was then refluxed for 2 hr. and cooled. The yellow sodio salt was removed by filtration and dried.

Anal. Calcd. for $C_3H_2N_2O_3SNa_2$: Na, 32.3. Found: Na, 32.5.

The yellow salt was resuspended in absolute alcohol and 0.045 mole of concentrated sulfuric acid was added. The mixture was stirred for several hours, then cooled, and the insoluble sodium sulfate removed. The alcohol was then evaporated, yielding a yellow residue. This residue was extracted with 35 ml. of hot water, filtered, and then concentrated to 5 ml. and cooled in a refrigerator. Yield of yellow crystals, 4.1 g. (72%); m.p. 174–175° (dec.).

Anal. Calcd. for $C_3H_2N_2O_2S$: C, 27.7; H, 1.54; N, 21.61. Found: C, 27.8; H, 2.15; N, 21.9.

Oxalylguanidine. To 25 ml. of anhydrous alcohol was added 3.04 g. (0.133 mole) of sodium and then 4.2 g. (0.044 mole) of guanidine hydrochloride. The salt which precipitated was removed and 6.46 g. (0.044 mole) of diethyloxalate was added to the alcoholic filtrate. This mixture was refluxed for 2 hr., then cooled, filtered, and the insoluble product removed.

Anal. Calcd. for $C_3H_3N_3O_3Na_2$: Na, 26.3. Found: Na, 26.4.

The salt was dissolved in water and then treated with an equivalent amount of concentrated sulfuric acid. A white solid separated which was insoluble in all the common solvents. Yield, m.p. 237° (in sealed tube).

Anal. Calcd. for $C_3H_5N_3O_3$: C, 27.5; H, 3.82. Found: C, 27.6; H, 3.85.

Ammonium oxalylguanide. Solution of oxalylguanidine in concentrated ammonium hydroxide and evaporation of the excess ammonium hydroxide solution gave a quantitative yield of the ammonium salt.

Anal. Calcd. for $C_3H_6N_4O_2$: C, 27.7; H, 4.62. Found: C, 27.8; H, 4.73.

3-Carbethoxy-2-oxobutanguanide (I). Two solutions, one containing 4.75 g. (0.04 mole) of guanidine hydrochloride in 30 ml. of absolute methanol and the other 1.15 g. (0.05 mole) of sodium in 30 ml. of absolute methanol were mixed, then filtered to remove the sodium chloride. To this solution was added 10 g. (0.05 mole) of diethyl α-oxalylpropionate and the mixture was refluxed for 3 hr. Upon returning to room temperature, 3 ml. of glacial acetic acid was added and the reaction product was set aside in the refrigerator overnight. The crystalline product was removed by filtration, washed with a small amount of anhydrous methanol, and then recrystallized from hot water; yield, 5.5 g. (51%) of a white crystalline material which had no definite melting point.

Anal. Calcd. for $C_8H_{13}N_3O_4$: C, 44.64; H, 6.09. Found: C, 44.5; H, 6.08.

5(4)-(2-Amino-4(5)-oxo-Δ²-imadazolineidene)-2-propanoic acid (II). Two grams of 3-carbethoxy-2-oxobutanguanide (I) was dissolved in 60 ml. of 6*N* hydrochloric acid and the solution was refluxed for 1.5 hr. The solution was then set

in a refrigerator overnight, and the product removed by filtration, yield, 580 mg. of silky needles melting with decomposition from 200–212°. A second crop of 50 mg. was obtained upon concentrating the mother liquors and allowing them to stand in a refrigerator overnight. The crude product upon recrystallization from water yielded a white crystalline powder which melted with effervescence at 234.5–235.5°. Total yield of recrystallized product 380 mg. (24.2%).

Anal. Calcd. for $C_6H_7N_3O_3$: C, 42.61; H, 4.17. Found: C, 42.6; H, 4.40.

Ethyl 5(4)-(2-amino-4(5)-oxo-Δ^2-imidazolineidene)-2-propionate. 5(4)-(2-Amino-4(5)-oxo-Δ^2-imidazolineidene)-2-propionic acid (II) (200 mg.) was dissolved in 9.1 ml. of 50% ethanol–concentrated sulfuric acid solution and the mixture then heated at 100° for approximately 20 min. The reaction vessel was then placed in an ice bath and upon cooling the *p*H was adjusted to approximately 8 with 6*N* ammonium hydroxide whereupon the ester precipitated. The product was removed by filtration and washed with several portions of cold water. Recrystallization of the crude material from 95% ethanol gave a yield of 120 mg. (51%) of a white crystalline material m.p. 275° dec.

An analytical sample was prepared by recrystallization from absolute ethanol. The sample was dried in an Abderhalden over phosphorus pentoxide at 110° for 2 hr.

Anal. Calcd. for $C_8H_{11}N_3O_3$: C, 48.71; H, 5.62. Found: C, 48.6; H, 5.7.

Ethyl 5(4)-(2-amino-4(5)-oxo-Δ^2-imidazoline)-2-propionate. Ethyl 5(4)-(2-amino-4(5)-oxo-Δ^2-imadazolineidene)-2-propionate (490 mg.) was dissolved in 100 ml. of glacial acetic acid. The solution was then hydrogenated at approximately 40 p.s.i. for 8 hr. using 100 mg. of Adams catalyst. Upon completion of the hydrogenation the solution was filtered and then concentrated to a syrup *in vacuo* (water pump). The *p*H was then adjusted to approximately 8 with 6*N* ammonium hydroxide whereupon the ester precipitated. The product was removed by filtration and the mother liquors when replaced in the refrigerator yielded a second crop.

The crude material was recrystallized from 95% ethanol yielding 220 mg. (45%) of a white crystalline material m.p. 227–229°.

Anal. Calcd. for $C_8H_{13}N_3O_3$: C, 48.23; H, 6.58. Found: C, 48.1; H, 6.74.

2-Amino-5-methyl-6-oxopyrimidine-4-carboxylic acid (III). To 7.5 ml. of 1*N* potassium hydroxide was added 340 mg. of 5(4)-(2-amino-4(5)-oxo-Δ^2-imidazolineidene)-2-propanoic acid and the mixture was heated on a steam bath for 30 min. After the heating period the solution was cooled, acidified with 6*N* hydrochloric acid, and set in the refrigerator to crystallize. The product was removed by filtration and recrystallized from hot water. The first crop of crystals weighed 130 mg. By concentrating the mother liquor a second crop of 80 mg. was obtained; total yield 62%. When a sample was placed on a melting point block at 285° and the temperature raised 0.5° per minute the melting point was 302° (dec.). An analytical sample was dried in an Abderhalden over phosphorus pentoxide at 110°.

Anal. Calcd. for $C_6H_7N_3O_3$: C, 42.61; H, 4.17. Found: C, 42.5; H, 4.31.

Ethyl hydantoidene-2-propionate. Ten grams (0.05 mole) of diethyl α-oxalylpropionate, 3 g. (0.05 mole) of urea, and 3.8 ml. of glacial acetic acid were placed in a flask equipped with a reflux condenser and a tube for introducing hydrogen chloride gas. The flask was heated on a steam bath while hydrogen chloride was bubbled through the mixture for 0.5 hr. The product was removed by filtration and washed with a small amount of water. The product was recrystallized from water yielding 4.3 g. (44%) of white powder melting at 181–181.5°.

Anal. Calcd. for $C_8H_{10}N_2O_4$: C, 48.48; H, 5.09. Found: C, 48.5; H, 5.17.

Hydantoidene-2-propanoic acid. Ethyl hydantoidene-2-propionate (340 mg.) was placed in 7.5 ml. of 1*N* potassium hydroxide and heated for 0.5 hr. at 100°. The solution was then cooled, neutralized with 6*N* hydrochloric acid and set aside to crystallize. The product after two recrystallizations from water yielded small white needles 175 mg. (61%) which melted at 278–280°. An analytical sample was dried in an Abderhalden over phosphorus pentoxide at 138° for 6 hr.

Anal. Calcd. for $C_6H_6N_2O_4$: C, 42.36; H, 3.56. Found: C, 42.1; H, 3.63.

2,6-Dioxo-5-methylpyrimidine-4-carboxylic acid. Hydantoidene-2-propanoic acid (1 g.) was dissolved in 23 ml. of 1*N* potassium hydroxide and the solution was then evaporated almost to dryness at 100° C. Upon cooling, the concentrate was acidified with 6*N* hydrochloric acid and allowed to stand in a refrigerator for several hours. The product (710 mg.) was removed by filtration and mother liquors were concentrated and cooled, yielding 270 mg. additional.

The two crops were combined and recrystallized from water yielding white crystalline needles. The first crop contained 405 mg., the second 200 mg. giving 60% over-all yield. The melting point depends upon the rate of heating of the melting point block. When a sample was placed on the block at 290° and the temperature raised 4°/minute, the sample decomposed with effervescence at 326.5–327.5°.

CORVALLIS, ORE.

[CONTRIBUTION FROM THE KEDZIE CHEMICAL LABORATORY OF MICHIGAN STATE UNIVERSITY]

Synthesis and Characterization of Nitraminotetrazoles[1]

JAMES A. GARRISON[2] AND ROBERT M. HERBST

Received July 16, 1956

The preparation of several 1-alkyl-5-nitramino- and 5-alkyl-nitraminotetrazoles is described. Comparison of the apparent dissociation constants and ultraviolet absorption spectra of these compounds and of 5-nitraminotetrazole indicates that the strong first dissociation of the latter is associated with the hydrogen of the nitramino group.

Recently 5-nitraminotetrazole was characterized as a dibasic acid with pK values of 2.5 and 6.1.[3] Since the two hydrogens in the structure do not necessarily occupy equivalent positions, it became of interest to determine whether the hydrogen attached to the tetrazole ring or the hydrogen of the nitramino group was responsible for the relatively strongly acidic character of the compound. Lieber *et al.*[4,5] have assigned the stronger acid function to the hydrogen of the nitramino group, a conclusion based on comparison of ultraviolet absorption spectra of 5-nitraminotetrazole and several of its salts with the spectra of nitramide and N-nitro-N′-aminoguanidine. Since corresponding data for other tetrazole derivatives were not available, it was thought that a more direct approach was needed to establish definitely which hydrogen was involved in the first dissociation of 5-nitraminotetrazole.

An analogy has been developed between the apparent acidity of 5-substituted tetrazoles, R—CN_4H, and carboxylic acids, R—COOH, and it has been shown that the nature of the group R affects the apparent acidic dissociation constant of the 5-substituted tetrazoles in much the same way as it affects the dissociation constant of the carboxylic acid.[6,7,8] Due to the instability of carbamic acid and most of its N-substituted derivatives, a direct comparison with the 5-aminotetrazoles is not feasible. Baur[9] has shown that 5-aminotetrazole behaves as a weak acid ($K_a = 5.73 \times 10^{-7}$; $pK_a = 6.24$). Acetylation of 5-aminotetrazole causes a marked increase in the acidic dissociation of the tetrazole group ($pK = 4.53$).[10] It would hardly be expected that the electron withdrawing effect of the acetyl group would be sufficiently great to endow the amidic hydrogen with strongly acidic character, and 5-acetylaminotetrazole behaves as a monobasic acid in aqueous media.

The introduction of a nitro group in place of one of the amino hydrogens of 5-aminotetrazole may be considered as acylation with a strongly electron withdrawing group. The resulting 5-nitraminotetrazole is capable of existing in a number of tautomeric forms (Fig. 1). It will be noted that forms D and E are identical, also, in form C, due to certain elements of symmetry in the 5-tetrazolyl system, the two hydrogens occupy equivalent positions on the ring and cannot be distinguished. The first dissociation of 5-nitraminotetrazole as a strong acid may involve either of two resonance hybrids of the tetrazole anion that can be developed from contributing forms (*a*) of the anion obtained by dissociation of the nuclear hydrogen or (*b*) resulting from dissociation of the nitramino hydrogen (Fig. 2).

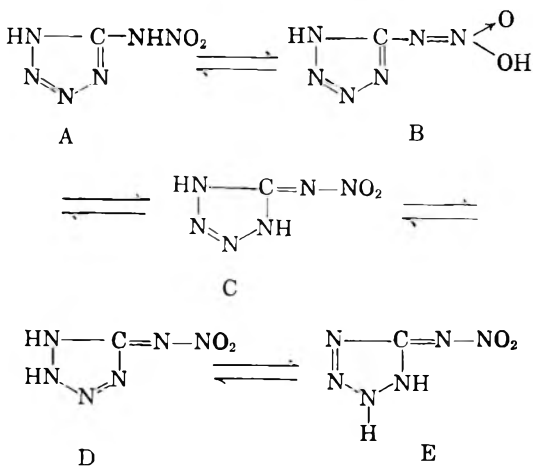


FIG. 1

In order to determine which type of resonance, Fig. 2 (*a*) or (*b*), predominated, two groups of monoalkyl nitraminotetrazoles were prepared and their physical properties studied. The first included 1-methyl-5-nitraminotetrazole (I) and 1-ethyl-5-nitraminotetrazole (II) in both of which only dis-

(1) Based on a thesis submitted to the School of Advanced Graduate Studies at Michigan State University in 1954 by James E. Garrison in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Parke, Davis Fellow in Organic Chemistry, 1952–1954. Present address: Mead Johnson and Company, Evansville, Ind.

(3) Herbst and Garrison, *J. Org. Chem.*, **18**, 941 (1953).

(4) Lieber, Patinkin, and Tao, *J. Am. Chem. Soc.*, **73**, 1792 (1951).

(5) Lieber, Sherman, and Patinkin, *J. Am. Chem. Soc.*, **73**, 2329 (1951).

(6) Mihina and Herbst, *J. Org. Chem.*, **15**, 1082 (1950).

(7) Garbrecht and Herbst, *J. Org. Chem.*, **18**, 1022 (1953).

(8) Herbst, in Graff, *Essays in Biochemistry*, John Wiley & Sons, Inc., New York, 1956, pp. 141–155.

(9) Baur, *Z. physik. Chem.*, **23**, 409 (1897).

(10) Herbst and Garbrecht, *J. Org. Chem.*, **18**, 1283 (1953).

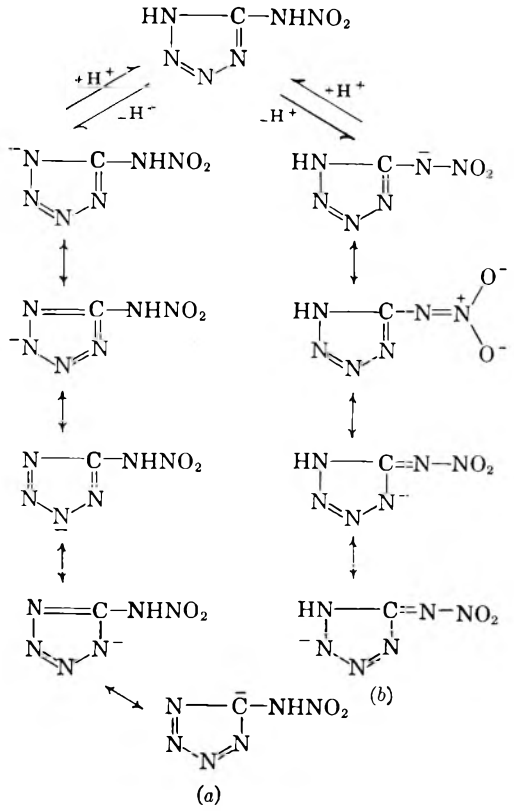
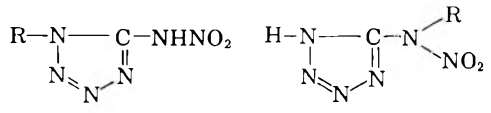


FIG. 2

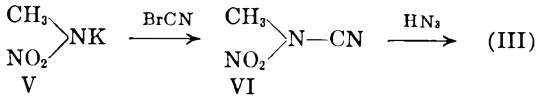
sociation and resonance of type (*b*) is expected; the second consisted of 5-methylnitraminotetrazole (III) and 5-ethylnitraminotetrazole (IV) in both of which only dissociation and resonance of type (*a*) is probable.



I. R = CH_3 III. R = CH_3
II. R = C_2H_5 IV. R = C_2H_5

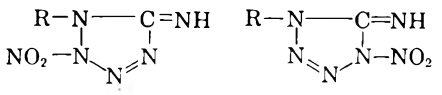
1-Methyl- and 1-ethyl-5-aminotetrazole and 5-methylamino- and 5-ethylaminotetrazole were prepared by the methods of Garbrecht and Herbst.[7,11] The corresponding alkyl nitraminotetrazoles were prepared by dehydration of the appropriate alkyl 5-aminotetrazole nitrates by adaptations of the procedure of Herbst and Garrison.[3] No attempt was made to find the optimum conditions for the preparation and isolation of the alkyl nitraminotetrazoles.

Since nitration of the 5-alkylaminotetrazoles could have taken place on the tetrazole ring in positions 1 or 2 with formation of 1-nitro- or 2-nitro-5-alkylaminotetrazoles, an independent synthesis of 5-methylnitraminotetrazole was carried out as follows: potassium methylnitramine (V), prepared according to Franchimont,[12] was treated with cyanogen bromide to form methylnitrocyanamide (VI). After interaction of VI and hydrazoic acid, III was isolated. The product was identical with the compound obtained by nitration of 5-methylaminotetrazole as shown by melting point, mixture melting point, infrared absorption spectrum and characterization as the 2-aminopyridine salt.



An attempt to characterize the product of nitration of 5-methylaminotetrazole by reduction to the corresponding hydrazino compound was unsuccessful. After hydrogenation of (III) only methylaminotetrazole, presumably formed by hydrogenolysis of the hydrazino compound, could be isolated.

The structure of 5-ethylnitraminotetrazole is assigned on the basis of analogy of method of preparation and similarity of properties with those of III. Although the structure of the 1-alkyl-5-nitraminotetrazoles is not supported by independent synthesis, it seems reasonable to assume that nitration of the 1-alkyl-5-aminotetrazoles follows a similar course, an assumption supported by the properties of the products, particularly their dissociation constants and ultraviolet absorption spectra. The 1-alkyl-5-nitraminotetrazoles are moderately strong acids (*p*K 2.7–2.8). Had nitration taken place on one of the ring nitrogens, a 1-alkyl-2-(or 4)-nitro-5-iminotetrazoline (VII) would have resulted. It is doubtful that ring nitration would have resulted in such strongly acidic compounds.



VIIa VIIb

The apparent dissociation constants of the alkyl nitraminotetrazoles are given in Table I. Both the 1-alkyl-5-nitramino- and the 5-alkylnitraminotetrazoles have *p*K values in the range 2.7–2.9. On the basis of dissociation constants resonance of either type (*a*) or (*b*) could explain the strong first dissociation of 5-nitraminotetrazole.

TABLE I

APPARENT DISSOCIATION CONSTANTS OF ALKYL 5-NITRAMINOTETRAZOLES

Compound	Apparent pK_1	Apparent $K_1 \times 10^3$
5-Nitraminotetrazole	2.55[a]	2.8[a]
I	2.72	1.9
II	2.74	1.8
III	2.88	1.3
IV	2.86	1.4

[a] The values for the second apparent dissociation constant are $pK = 6.04$, $K = 9.1 \times 10^{-7}$.

(11) Garbrecht and Herbst, *J. Org. Chem.*, 18, 1014 (1953).

(12) Umbgrove and Franchimont, *Rec. trav. chim.*, 15, 195 (1895).

Since both the nuclear and the nitramino hydrogen dissociate with equal ease, methods other than measurement of the dissociation constants were needed to differentiate between dissociations and resonance of type (*a*) and (*b*). 5-Nitraminotetrazole exhibits strong absorption in the ultraviolet with a maximum at 277–278 mμ and a minimum at 237 mμ.[3,5] The 5-alkylnitraminotetrazoles should be almost completely dissociated in aqueous solution to a tetrazole anion of type (*a*), while the 1-alkyl-5-nitraminotetrazoles should be almost completely dissociated to a tetrazole anion of type (*b*). Resonance hybrids of types (*a*) and (*b*) should show differences in their ultraviolet absorption. Furthermore, since both tetrazole anions are formed from relatively strong acids, conversion to the sodium or potassium salts should cause little, if any, change in the ultraviolet absorption. These considerations were realized. Both I and II and their potassium salts exhibited a maximum at 277–278 mμ and a minimum at 237 mμ. On the other hand, III and IV and their potassium salts exhibited a maximum at 246 mμ; the minimum was out of the range of the instrument. Since the maxima and minima of 5-nitraminotetrazole, I and II, both as such and as potassium salts, are identical, it may be concluded that the hydrogen of the nitramino group of 5-nitraminotetrazole is responsible for the first dissociation of this compound with a tetrazole anion of type (*b*) forming. The ultraviolet absorption of 5-nitraminotetrazole in a large excess of potassium hydroxide solution, in which it should exist as a doubly charged anion, is very similar to the spectra in aqueous solution of both itself and the 1-alkyl-5-nitraminotetrazoles. The maximum is shifted toward shorter wave lengths, 271–272 mμ for the doubly charged anion as compared with 277–278 mμ for the singly charged anion; the minima are 232 mμ and 237 mμ, respectively. The results indicate that resonance of type *b* is modified by the second negative charge but still predominates.

The four alkyl nitraminotetrazoles were further characterized as potassium salts, 2-aminopyridine salts, and by infrared absorption spectra (Fig. 3).

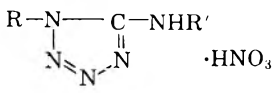
EXPERIMENTAL[13]

Alkyl 5-aminotetrazoles. 1-Methyl- and 1-ethyl-5-aminotetrazole were prepared from the appropriate alkyl cyanamides by interaction with hydrazoic acid.[11] 5-Methylamino- and 5-ethylamino-tetrazole were prepared by hydrogenolysis of 5-benzylmethylamino- and 5-benzylethylaminotetrazole.[7,14]

Alkyl 5-aminotetrazole nitrates. The appropriate alkyl 5-aminotetrazole was added with cooling to concentrated nitric acid (sp. gr. 1.419) in 1:1.5 molar proportion. The mixture was warmed gently, avoiding overheating, until all the tetrazole had dissolved. The nitric acid salt which separated on cooling was filtered, washed with ethyl ether and used without crystallization. Melting points and analyses are given in Table II.

TABLE II

ALKYL 5-AMINOTETRAZOLE NITRATES



R	R′	M.P., °C.	Formula	Analysis: Calculated C	Calculated H	Calculated N	Found C	Found H	Found N
CH_3	H	158–160	$C_2H_6N_6O_3$	14.8	3.7	51.8	15.2	3.6	51.9
C_2H_5	H	125–127	$C_3H_8N_6O_3$	20.5	4.6	47.7	20.7	4.5	47.6
H	CH_3	70–72	$C_2H_6N_6O_3$	14.8	3.7	51.8	14.6	3.6	51.9
H	C_2H_5	68–70	$C_3H_8N_6O_3$	20.5	4.6	47.7	20.8	4.8	47.2

1-Methyl-5-nitraminotetrazole (I). To 8 ml. of ice cold concentrated sulfuric acid was added 6.9 g. (0.023 mole) of 1-methyl-5-aminotetrazole nitrate. The mixture was allowed to warm slowly to 20° and then poured slowly onto 50 g. of ice. After about 90% of the sulfuric acid had been neutralized by addition of the calculated amount of potassium hydroxide, the aqueous solution was extracted with ether in a continuous extractor for three days. The ether solution was separated, dried over sodium sulfate, and evaporated to about 100 ml. on a steam bath. The remaining ether was removed at room temperature in a current of dry air. The solid residue was recrystallized by dissolving in a small amount of ethyl acetate and adding four volumes of petroleum ether. Yield, 1.9 g. (31%), m.p. 129–130°.

Anal. Calcd. for $C_2H_4N_6O_2$: C, 16.7; H, 2.8; N, 58.3. Found: C, 16.8; H, 2.7; N, 58.1.

1-Ethyl-5-nitraminotetrazole (II). Five grams of 1-ethyl-5-aminotetrazole nitrate was dissolved in 100 ml. of cold concentrated sulfuric acid by addition in small portions so that the temperature did not rise above 10°. The mixture was allowed to warm slowly to 20° and then poured into 150 ml. of ice cold ether. The sulfuric acid was further extracted with two 150-ml. and four 50-ml. portions of ether. The combined extracts were evaporated to dryness at room temperature. The crude product was recrystallized from benzene. Yield, 1.15 g. (26%), m.p. 102–103°.

Anal. Calcd. for $C_3H_6N_6O_2$: C, 22.8; H, 3.8; N, 53.1. Found: C, 23.1; H, 3.7; N, 53.0.

5-Methylnitraminotetrazole (III). (*a*) 5-Methylaminotetrazole nitrate (6.5 g., 0.04 mole) was added slowly with cooling and stirring to 5.5 ml. of ice cold concentrated sulfuric acid. The mixture was allowed to stand in an ice

(13) All analyses were done by Micro-Tech Laboratories, Skokie, Ill.

(14) Finnegan, Henry, and Lieber, *J. Org. Chem.*, **18**, 779 (1953); Garbrecht and Herbst, *J. Org. Chem.*, **18**, 1269 (1953).

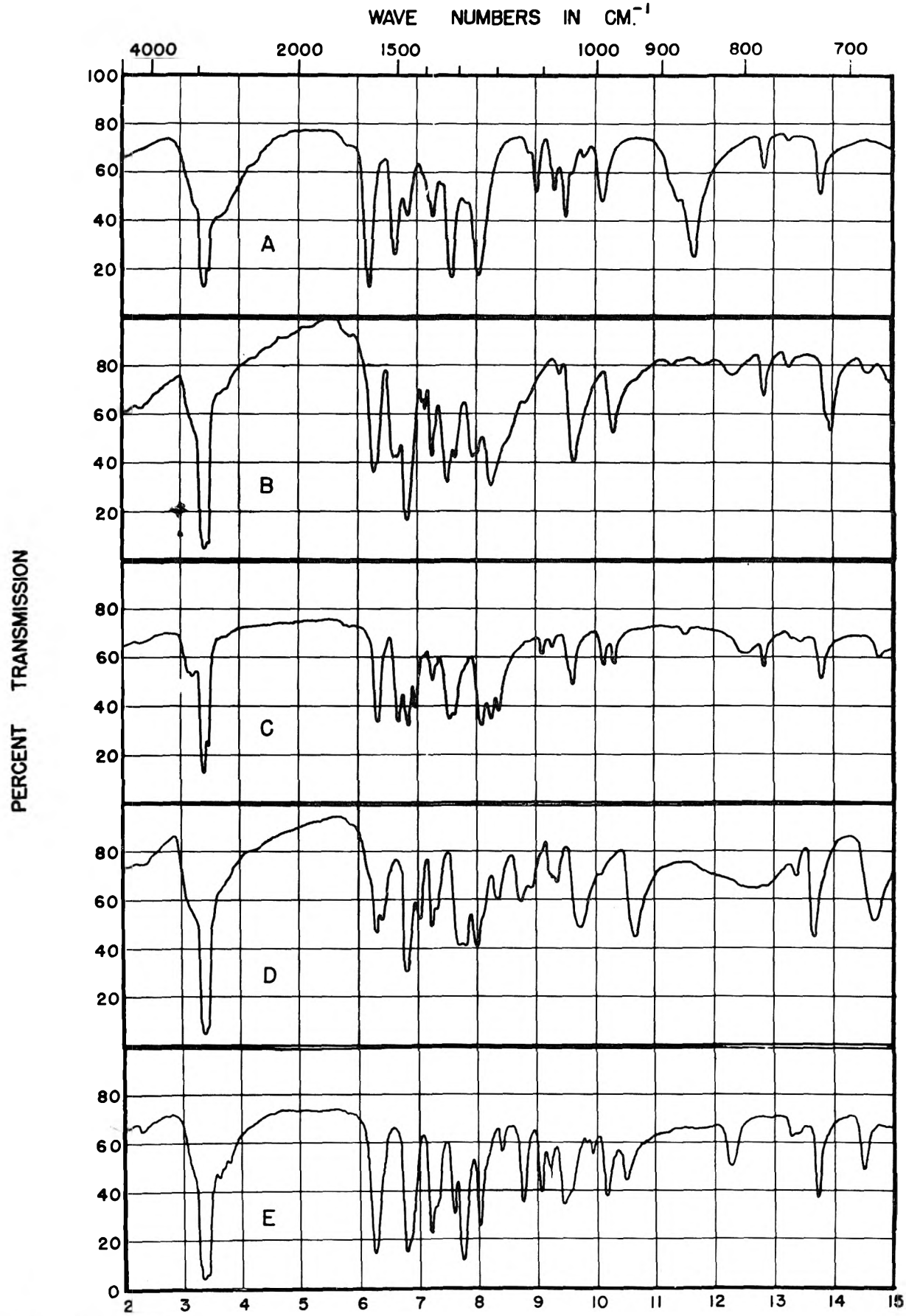


FIG. 3.—INFRARED ABSORPTION SPECTRA IN WHITE MINERAL OIL MULLS OF (A) 5-Nitraminotetrazole; (B) 1-Methyl-5-Nitraminotetrazole; (C) 1-Ethyl-5-nitraminotetrazole; (D) 5-Methylnitraminotetrazole; (E) 5-Ethylnitraminotetrazole.

bath for 15 min. and then poured onto 30 g. of ice. (On one occasion the product crystallized from the aqueous acid solution but this could not be repeated.) The aqueous solution was extracted with two 150-ml. and three 50-ml. portions of ether. The combined ethereal extracts were dried over sodium sulfate and evaporated to dryness at room temperature. The residue was recrystallized by dissolving in the minimum volume of ethyl acetate and adding three volumes of petroleum ether. Yield, 2.0 g. (35%), m.p. 112–113°.

Anal. Calcd. for $C_2H_4N_6O_2$: C, 16.7; H, 2.8; N, 58.3. Found: C, 16.7; H, 3.0; N, 58.0.

(*b*) Forty grams of N,N'-dinitrodimethyloxamide[12] was treated with 160 ml. of concentrated aqueous ammonia (sp. gr. 0.899). The mixture warmed spontaneously to about 40°. After cooling to room temperature the mixture was made slightly acid to Congo red with 10% sulfuric acid. The colorless precipitate of oxamide was removed by filtration and the filtrate was extracted with three 100-ml. portions of ether. An equivalent amount of potassium hydroxide dissolved in 100 ml. of methanol was added to the ethereal extracts. Upon evaporation of the solution to a small volume potassium methylnitramine separated as a colorless powder. Yield, 18 g., m.p. 220°.[12]

One-tenth mole (11.4 g.) of potassium methylnitramine suspended in 50 ml. of methanol was treated with 10.6 g. (0.1 mole) of cyanogen bromide in 100 ml. of ether. The solution was filtered to remove potassium bromide and the filtrate evaporated to a small volume at room temperature. At this point the mixture separated into two layers. The upper, water-insoluble layer was assumed to be methylnitrocyanamide. The product was not purified.

Four grams of crude methylnitrocyanamide was dissolved in 25 ml. of a 13% solution of hydrazoic acid in benzene and allowed to stand at room temperature for two days when an additional 25 ml. of hydrazoic acid solution was added and the mixture boiled under reflux for 2 hr. After cooling and evaporating to a small volume at room temperature, 100 ml. of petroleum ether was added. The mixture separated into two layers, the upper, petroleum ether layer, was decanted and the lower layer was dissolved in ethyl acetate. After dilution of the ethyl acetate solution with four volumes of petroleum ether, the product separated slowly as long, colorless needles, m.p. 113–114°. The material was identical with III as prepared in (*a*) as shown by mixture melting point, infrared spectrum, and identity of the 2-aminopyridine salts.

5-Ethylnitraminotetrazole (IV). 5-Ethylaminotetrazole nitrate (2.0 g.) was dissolved in 2.0 ml. of cold concentrated sulfuric acid. The cold solution was poured over 20 g. of ice, the aqueous solution was then extracted twice with 100-ml. portions of ether, the ethereal extracts dried over sodium sulfate and evaporated to dryness at room temperature. The residue was dissolved in the minimum volume of cold ethyl acetate and the clear solution diluted with a large volume of petroleum ether. IV separated as colorless plates, yield 0.7 g. (25%), m.p. 88–89°.

Anal. Calcd. for $C_3H_6N_6O_2$: C, 22.8; H, 3.8; N, 53.1. Found: C, 22.7; H, 4.0; N, 53.2.

Reduction of 5-methylnitraminotetrazole. 5-Methylnitraminotetrazole (1.44 g., 0.01 mole) was dissolved in 50 ml. of absolute ethanol and reduced with hydrogen at 50 p.s.i. using palladium oxide catalyst. When three molar equivalents of hydrogen had been absorbed, the reduction was stopped and the catalyst removed by filtration. The alcoholic solution was treated with 1.06 g. of benzaldehyde and evaporated to dryness. The residue was recrystallized twice from 1,4-dioxane. Elemental analysis and mixture melting point indicated that the product was 5-methylaminotetrazole. Yield 0.5 g. (50%), m.p. 185–187°. (The product resolidified on further heating and remelted at 224–225°.)[14]

Anal. Calcd. for $C_2H_5N_5$: C, 24.2; H, 5.1; N, 70.7. Found. C, 24.4; H, 5.1; N, 70.4.

Potassium salts of alkyl nitraminotetrazoles. The potassium salts were prepared by dissolving the alkyl nitraminotetrazole in ether and adding methanolic potassium hydrox-

TABLE III

2-Aminopyridine Salts of Alkyl Nitraminotetrazoles

2-Aminopyridine Salt of	M.P., °C.	Formula	Analysis					
			Calculated			Found		
			C	H	N	C	H	N
I	177–178	$C_7H_{10}N_8O_2$	35.3	4.2	47.0	35.5	4.4	46.8
II	131–132	$C_8H_{12}N_8O_2$	38.1	4.8	44.4	38.2	4.7	44.2
III	165–167	$C_7H_{10}N_8O_2$	35.3	4.2	47.0	35.1	4.2	47.1
IV	139–140	$C_8H_{12}N_8O_2$	38.1	4.8	44.4	38.5	5.1	44.1

TABLE IV

Ultraviolet Absorption of Alkyl Nitraminotetrazoles and Their Potassium Salts in 1×10^{-4} Aqueous Solution

Compound	Ultraviolet Absorption			
	Maximum		Minimum	
	mμ	$\epsilon \times 10^{-3}$	mμ	$\epsilon \times 10^{-3}$
5-Nitraminotetrazole	277	(1.285)[a]	237	(0.131)[a]
I	277	9.77	237	2.9
II	277	9.90	237	2.72
III	246	4.70	—	—
IV	246	4.95	—	—
Potassium 5-nitraminotetrazole	277[b]		237[b]	
Potassium I	277	8.10	236	2.42
Potassium II	277	7.93	236	2.51
Potassium III	246	5.29	—	—
Potassium IV	246	5.09	—	—
Dipotassium 5-nitraminotetrazole	272	6.09	230	2.64

[a] $\epsilon \times 10^{-4}$. [b] Reference 5.

ide until precipitation was complete. The salts were filtered off and recrystallized from ethyl acetate. Yields were quantitative. The potassium salts decompose explosively at, or near, their melting points which are as follows: potassium I, 170–171°; potassium II, 205–206°; potassium III, 191–192°; potassium IV, 174–175°. Due to the explosive nature of these salts they were not subjected to elemental analysis. Ultraviolet spectra of the salts were identical with those of the free alkyl nitraminotetrazoles in water or in an equivalent amount of dilute potassium hydroxide solution.

2-Aminopyridine salts of alkyl nitraminotetrazoles were prepared by treating an ethereal solution of the appropriate alkyl nitraminotetrazole with an equivalent amount of 2-aminopyridine dissolved in ether and recrystallizing from 1:1 isopropyl alcohol-ethyl alcohol. Yields were quantitative. Melting points and analyses are given in Table III.

Potentiometric titrations were done using a Beckman Model G *p*H meter. Approximately 0.01 molar solutions of the alkyl nitraminotetrazoles in water were titrated with standard 0.1*N* aqueous potassium hydroxide at 25 ± 0.02°. The results are summarized in Table I.

Ultraviolet absorption spectra were determined with a Beckman model DU spectrophotometer with approximately 1×10^{-4} molar aqueous solutions of the alkyl nitraminotetrazoles or their potassium salts. Spectra of the alkyl nitraminotetrazoles in an equivalent amount of aqueous potassium hydroxide and of 5-nitraminotetrazole with two equivalents of aqueous potassium hydroxide were also determined. The location of maxima and minima and extinction coefficients is given in Table IV.

EAST LANSING, MICH.

[CONTRIBUTION FROM THE COURTAULD INSTITUTE OF BIOCHEMISTRY]

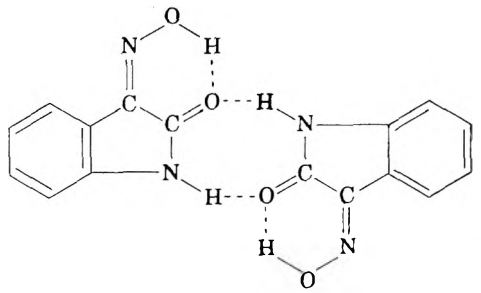
Vibrational Frequencies of Isatin Oximes

D. G. O'SULLIVAN AND P. W. SADLER

Received August 22, 1956

The infrared spectra of a set of substituted isatin-β-oximes and related compounds indicate that the former contain both intra- and intermolecular hydrogen bonding. Comparatively large shifts in the α-carbonyl group stretching frequencies occur with variation in ring substituents similar to the shifts observed with substituted oxindoles and with substituted acetanilides in the solid state. These shifts increase with the appropriate σ values of the substituents. Frequencies associated with the oxime group occur near 1660, 1200, and 1000 cm.$^{-1}$ and are referred to C=N stretching, N—O—H deformation and N—OH stretching modes, respectively. The 1660 cm.$^{-1}$ band is of variable intensity. The medium intensity deformation mode decreases in frequency with increase in the σ value of the substituent, while the 1000 cm.$^{-1}$ band is the strongest in the spectrum and increases in frequency with the σ value. Lower frequency ring vibrations are correlated with the substitution pattern.

Few systematic data are available on the infrared spectra of oximes. Palm and Werbin[1] found that α- and β-oximes in nujol mulls possessed associated OH stretching frequencies near 3250 and 3150 cm.$^{-1}$, respectively, and bands near 1650, 1300, and 920 cm.$^{-1}$ which were ascribed to C=N stretching, OH deformation and N—OH stretching vibrations. Duyckwerts[2] provided further data in a study of some oximes and their metal coordination complexes. Substituted isatin-β-oximes were examined for information on their structure, on the position of bands characteristic of the oxime group and for the effect of substituents on these frequencies. A number of possible isomeric structures exist for these compounds, together with a considerable variety of hydrogen-bonded association complexes. Infrared results obtained with isatin-β-oximes substituted in the benzene ring are consistent with the assumption that formula I represents the structure and mode of association of compounds of this type. Other association forms appear less likely.



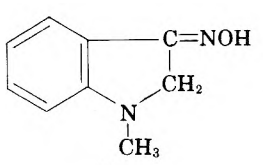
I

Free OH and NH stretching absorptions, to be expected near 3650 and 3450 cm.$^{-1}$, respectively, are absent from all oximes in Table I. Intense absorption near 1720 cm.$^{-1}$, produced by the stretching vibrations of the carbonyl group, and the presence, in some cases, of a C=N stretching frequency near 1660 cm.$^{-1}$ confirm the usually ascribed molecular structures, but the existence of an intense and broad band between 3200 and 2600 cm.$^{-1}$ indicates that the structures are involved in extensive hydrogen bonding. N-Methylindoxyl oxime II, which can associate only through the oxime groups, possesses a broad band of medium intensity with a fairly sharp maximum at 3210 cm.$^{-1}$ in accordance with the behavior of simpler oximes.[1] The sharp and lower intensity band at 2922 cm.$^{-1}$ in both N-methylindoxyl oxime and isatin is produced by CH stretching vibration. Remaining compounds in Table I possess an intense broad band near 3200

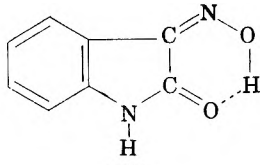
(1) A. Palm and H. Werbin, *Can. J. Chem.*, 31, 1004 (1953).

(2) G. Duyckwerts, *Bull. soc. roy. sci. Liège*, 21, 196 (1952).

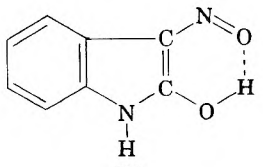
cm.$^{-1}$ and a broad band of slightly lower intensity near 2900 cm.$^{-1}$ The former occurs in the region characteristic of the CO...H—N linkage as illustrated in Table I by isatin. This and the absence of a free NH frequency near 3450 cm.$^{-1}$ in the oximes agree with the suggestion that the 3200 cm.$^{-1}$ band is, at least in part, produced by an amide type of association. The presence of a similar, but somewhat less intense, band in N-methylisatin oxime, in which amide association is absent, indicates that the 3200 cm.$^{-1}$ band does not arise entirely from this cause. The absorption near 2900 cm.$^{-1}$ is too intense and broad to be attributed solely to the CH frequency and must also be referred to association involving the oxime group. An OH stretching absorption at this low wave number implies that hydrogen bonding in these compounds is stronger than is usually the case in simpler oximes. This strengthening can be achieved by resonance involving III and IV producing an intramolecularly-bonded hybrid. Structure III must be the main contributor as all the compounds possess strong carbonyl absorptions, but the latter are displaced to lower frequencies than that of isatin, confirming the increase in single bond character of this group. Further confirmation arises from the appearance of a single very broad weak band between 3200 and 2600 cm.$^{-1}$ in both N-methylisatin oxime and 5-methylisatin oxime when the compounds were examined in chloroform solution. Intramolecular hydrogen bonding should not be markedly affected under these conditions.



II



III



IV

Table I shows that, if the 5-methoxy compound is excluded, the carbonyl frequency increases with the σ value[3] of the substituent taken with reference to the NH group, indicating that the normal effect of the substituents is transmitted to the carbonyl group *via* the NH group as in substituted acetanilides[4] and oxindoles.[5]

The C=N stretching frequency near 1650 cm.$^{-1}$ is variable. Occasionally it is split into two very weak peaks and frequently it is absent. Intense absorption on either side of this region may obscure the absorption produced by the C=N group in some cases. No correlation exists between this frequency and the σ constants of substituents with respect to this position. A number of maxima occur near 1300 cm.$^{-1}$ but no characteristic absorption referable to the oxime group appears to exist in this neighborhood. Many types of vibration such as Ar—N, Ar—C, and other ring frequencies and CO deformation modes may be responsible for these peaks which are listed, together with the benzene ring frequencies near 1620, 1480, and 1450 cm.$^{-1}$, in Table II. A number of frequencies related to substituents also occur in this region, such as the strong asymmetric and symmetric NO_2 stretching absorptions at 1526 and 1350 cm.$^{-1}$ in 7-nitroisatin oxime. However, at about 1200 cm.$^{-1}$ strong or medium absorption occurs in all the isatin oximes, which is much more intense than that feature of ortho disubstituted benzenes, the weak maximum at 1208 cm.$^{-1}$ which is present in isatin. As shown in Table III the frequencies tend to decrease with increase in the σ values of the substituents in virtue of their position in relation to the Ar—C linkage. This absorption is provisionally referred to the N—O—H bending vibration. All the oximes show absorption in the 1020 cm.$^{-1}$ region which is usually the most intense absorption in the spectrum. This band is completely absent in the parent ketones and is undoubtedly characteristic of the oxime group in this series. These frequencies appear to increase with the σ constants of the substituents as shown in Table III. They are probably produced by the N—OH stretching mode, as the C—OH stretching frequency in alcohols is responsible for a strong band in the 1200 to 1000 cm.$^{-1}$ region. The strong band near 980 cm.$^{-1}$ reported by Palm and Werbin[1] is likely to be shifted to higher frequencies in isatin oximes, one contributing cause being the

TABLE I

HAMMETT'S σ VALUES WITH REFERENCE TO THE Ar-NH LINKAGE AND CO FREQUENCIES OF ISATIN-β-OXIMES

Substituent	M.P., °C.	σ	Frequency[a]
5-MeO	248	−0.268	1734
5-Me	248	−0.170	1710
6-Me	230	−0.069	1712
None	224	0	1712
5-F	282	0.062	1712
6-F	240	0.337	1720
6-I	195	0.352	1725
6-Cl	255	0.373	1727
6-Br	244	0.391	1727
7-Br	263	—	1733
7-NO_2	>300	—	1731
1-Me	194	—	1703
Compound			
Isatin	203	—	1730

[a] All peaks are of high intensity.

(3) L. P. Hammett, *Physical Organic Chemistry*, McGraw-Hill, New York, 1940, p. 188.

(4) D. G. O'Sullivan and P. W. Sadler, *J. Org. Chem.* (in the press).

(5) A. E. Kellie, D. G. O'Sullivan, and P. W. Sadler, *J. Chem. Soc.* (in the press).

TABLE II

FREQUENCIES IN THE 1630 TO 1250 CM.$^{-1}$ REGION

Substituent								
None	1621 s			1467 s	1393 w		1350 s	1301 w
1-Me	1617 s		1498 w	1460 m	1385 m		1348 m	1318 vw
5-MeO	1607 m		1489 s	1444 w	1400 vw		1320 m	1303 m
5-Me	1630 m		1482 m	1446 w	1403 vw		1324 m	
5-F	1621 s		1478 s	1458 s	1408 w		1330 m	
6-Me	1630 s			1450 m			1355 m	1300 vw
6-Br	1616 s		1478 m	1440 s		1362 m	1341 m	1290 w
6-I	1615 s		1478 m	1437 m		1360 m	1342 m	1290 w
7-Br	1621 s		1480 w	1437 s			1342 s	
7-NO_2	1626 s	1526 s	1474 s	1445 w	1398 vw	1350 m	1334 s	
Compound								
Isatin	1620 s			1469 m	1405 w		1338 m	1295 w
II[a]	1616 m		1481 m	1433 w	1382 vw		1343 m	

[a] N-methylindoxyl oxime.

TABLE III

FREQUENCIES BELOW 2000 CM.$^{-1}$ ASSOCIATED WITH THE OXIME GROUP

Substituent	σ	Frequencies									
6-Me	−0.170				1240 m		1200 m		1025 s		
5-Me	−0.069	1665 vw		1656 vw		1217 m			1025 s		
None	0		1662 m		1220 m		1195 m		1030 s		
5-MeO	0.115	1672 w		1640 w		1207 s		1042 s		1026 s	
6-Br	0.232				1210 w		1194 m	1065 m		1030 s	
6-I	0.276		1640 m			1200 m			1033 s		
5-F	0.337					1197 s		1050 s		1036 s	
7-Br	0.391		1640 m			1181 s			1040 s		
7-NO_2	0.710		1697 m		1210 m		1180 w	1052 s		1030 s	
1-Me	—					1201 w			1021 s		
Compound											
II[a]	—	1668 vw		1654 vw		1206 vw			1000 m		

[a] N-Methylindoxyl oxime.

TABLE IV

REMAINING FREQUENCIES BELOW 1200 CM.$^{-1}$ CLASSIFIED WITH SUBSTITUTION PATTERNS

Compound									
(A) 1,2-Disubstituted Benzenes									
II[a]	1154 w	1081 w	957 w	862 vw	785 vw	749 w	708 vw		660 vw
B[b]	1156 w	1080 m	981 m	858 vw	781 w	749 m	727 w		700 w
C[c]	—	1100 w	940 vw	888 vw	788 s	751 s	732 w	716 w	650 m
D[d]	1150 w	1101 m	951 w	890 w	774 w	740 w	—		663 w
(B) 1,2,3-Trisubstituted Benzenes									
Substituent[e]									
7-Br	1140 s	886 vw		820 m	799 m	760 w	737 m		686 m
7-NO_2	—	930 w		817 w	785 m	743 s	705 w		690 m
(C) 1,2,4-Trisubstituted Benzenes									
Substituent[e]									
5-Me	1150 w	1128 vw	—	—	820 m	783 vw	737 w	670 w	640 w
5-MeO	1178 w	1130 vw	914 vw	881 w	817 m	780 w	735 m	671 w	645 m
5-F	1155 s	1114 w	928 m	890 m	833 m 823 m	784 m	738 m	672 w	639 m
6-Me	1153 m	1124 m	951 vw	873 vw	822 m	788 w	738 w	—	666 m
6-Br	—	1115 m	910 m	864 w	822 m	780 vw	760 w	693 w	665 m
6-I	—	1121 m	903 m	865 w	821 m	—	760 w 734 w	685 w	662 m

[a] N-Methylindoxyl oxime. [b] N-Methylisatin oxime. [c] Isatin oxime. [d] Isatin. [e] All these compounds are substituted isatin oximes.

increased strength of the hydrogen bonding in the latter compounds.

Most peaks below 1180 cm.$^{-1}$ are produced by vibrations involving the basic ring skeleton and the attached hydrogen atoms. These frequencies appear to be primarily related to the substitution pattern and are less dependent on the type of substituents. This is shown in Table IV in which, for convenience, these substances are classified as substituted benzenes in terms of their substitution type.

EXPERIMENTAL

Spectra were obtained in potassium bromide disks because of the insolubility of most of the compounds in suitable solvents. The instrument used was a Perkin-Elmer 21 double-beam recording spectrometer with a rock-salt prism.

Compounds. Substituted isatin oximes were prepared from the corresponding isatins[6-8] in the usual way.

N-Methylindoxyl oxime. N-Methyl-O-acetylindoxyl was dissolved in excess hot 2*N* sodium hydroxide under nitrogen. Sufficient aqueous hydroxylamine hydrochloride was then added to neutralize the solution. The oxime, m.p. 208°, was collected and crystallized from aqueous ethanol.

LONDON, ENGLAND

(6) P. W. Sadler, *J. Org. Chem.*, 21, 169 (1956).
(7) P. W. Sadler and R. L. Warren, *J. Am. Chem. Soc.*, **78**, 1251 (1956).
(8) D. G. O'Sullivan and P. W. Sadler, *J. Chem. Soc.*, 2202 (1956).

[CONTRIBUTION FROM THE PHYSICAL RESEARCH LABORATORY AND THE SPECTROSCOPY LABORATORY,

THE DOW CHEMICAL COMPANY]

Evidence for Esters of *Aci*-Nitrocyclohexane as Intermediates in Production of Cyclohexanone Oxime

ROBERT E. McCOY AND ROLAND S. GOHLKE

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Processes yielding cyclohexanone oxime by reactions of *aci*-nitrocyclohexane salts with an alcohol and an acid and with an alkyl halide were recently disclosed. It is proposed that these reactions proceed *via* an unstable ester of *aci*-nitrocyclohexane. To test this hypothesis, salts of *aci*-nitrocyclohexane were treated with alkyl sulfates. As anticipated, cyclohexanone oxime was the principal product. Attempts to isolate the esters in these reactions have failed. Titrimetric data suggest that the reaction of *aci*-nitrocyclohexane with alcohols is esterification. Only three types of reagents are known to convert *aci*-nitrocyclohexane or its salts to cyclohexanone oxime; in each case an ester of *aci*-nitrocyclohexane is a logical intermediate.

Hamann and Bauer obtained cyclohexanone oxime and an aldehyde or ketone by reaction of nitrocyclohexane with a base and a primary or secondary alkyl halide.[1] Welz and Weise obtained oximes, especially cyclohexanone oxime, by gradual addition of salts of the corresponding nitroparaffins to acidified alcohols.[2]

It is proposed here that the path of reaction in the first case involves formation of a salt of *aci*-nitrocyclohexane, its conversion to an ester of *aci*-nitrocyclohexane by reaction with the alkyl halide, and the rapid decomposition of this unstable ester to give cyclohexanone oxime and a carbonyl compound. In the second case it is proposed that the path of reaction involves formation of the *aci*-nitro compound on addition of the salt to the acid medium, esterification of the *aci* form, and decomposition of the ester.[3] If these hypotheses are correct, it follows that reaction of salts of *aci*-nitrocyclohexane with alkyl sulfates, which should effect alkylation of the *aci* form, will also produce cyclohexanone oxime.

It was found, as predicted, that reaction of methyl or ethyl sulfate with the sodium, potassium, or calcium salt of *aci*-nitrocyclohexane yielded cyclohexanone oxime as the principal product. Yields as high as 76% were obtained by reaction of methyl sulfate with the sodium salt of *aci*-nitrocyclohexane in methanol.

In an attempt to obtain further evidence that the esters of *aci*-nitrocyclohexane are intermediates in the production of cyclohexanone oxime, this reaction and those of the prior authors[1,2] were repeated at 0° and at dry-ice temperature. It was hoped to retard decomposition of the ester sufficiently to permit its detection, but this was not realized.[7]

Dilute solutions of *aci*-nitrocyclohexane salts in

(1) Hamann and Bauer, German Patent 825,547 (1951).
(2) Welz and Weise, German Patent 837,692 (1952).
(3) The suggested path of reaction is similar to that observed with certain nitro compounds[4-6] in which the C=N bond of the *aci* form is conjugated with at least one benzene ring or multiple bond. In these cases both the *aci* form and the ester are generally sufficiently stable that their identification is relatively simple, in distinct contrast to the corresponding derivatives of nitrocyclohexane.
(4) Bamberger, *Ber.*, **34**, 589 (1901).
(5) Nenitzescu and Isacescu, *Ber.*, **63**, 284 (1930); *Bull. Chem. Soc. Rom.*, **14**, 53 (1932).
(6) Arndt and Rose, *J. Chem. Soc.*, 1, (1935).
(7) This failure may have been due to lack of analytical equipment designed for operation below room temperature. The samples could be kept cold only until the analytical instruments were loaded.

methanol and ethanol were acidified with hydrochloric acid and titrated immediately with base on a *p*H recorder. A large portion of the theoretical amount of *aci*-nitrocyclohexane did not appear in the titration but disappeared irreversibly.[8] The titration curves are strikingly similar to those of mixtures of hydrochloric and acetic acid in the alcohols. Although this suggests that the disappearance of *aci*-nitrocyclohexane, like that of acetic acid, results from esterification, the ester could not be identified in these solutions. The mass spectra (obtained at an inlet temperature of 100° C.) revealed the presence of cyclohexanone oxime.

So far as the authors are now aware, no organic compound other than an alcohol, an alkyl halide, or an alkyl sulfate has been reported to convert nitrocyclohexane to cyclohexanone oxime, and these reagents must act on the *aci* form or its salt to accomplish this result.[9] In all of these reactions, therefore, it is reasonable to assume as common intermediates the esters of *aci*-nitrocyclohexane.[10]

EXPERIMENTAL

Materials. Nitrocyclohexane obtained from the Union Oil Co. of California had been steam distilled by the supplier. Infrared and mass spectra indicated good purity, and a pale yellow color was not objectionable; it was used without further treatment. Nitrocyclohexane from Du Pont was from pilot plant production. Analyses indicated purity similar to that of the other material, but upon standing several months a deep color developed. Therefore most of this sample was subsequently repurified by distillation. A colorless product boiling at 100.5° at 25 mm. was obtained. Aside from intensity of colors no significant differences in behavior of the various nitrocyclohexane samples were observed. Standard reagent grade chemicals, solvents purified by distillation, and de-ionized water were used throughout these investigations.

Reaction of dialkyl sulfates with salts of nitroparaffins. In one of the best experiments 0.1 mole sodium salt of nitrocyclohexane was prepared in 100 ml. methanol. This mixture was heated to reflux, and a mixture of 10 ml. dimethyl sulfate and 40 ml. methanol was added dropwise. Two hours later a little concentrated ammonia was added to destroy any excess methyl sulfate. The yield of cyclohexanone oxime, determined from mass spectrometer analysis of the solution, was about 76 per cent.

For purposes of determining the effect of different variables on the yield, the solutions produced in a large number of experiments were analyzed by mass spectrometry and the calculated yields were compared. (The identification of the compounds from their mass spectra is explained at the end of the Experimental section.) Yields calculated from mass spectra in this series of experiments exceeded those obtained by isolation in a few trials by about 10–15%. This is considered a measure of the loss in isolating the product from the complex reaction mixture, and the mass spectrometer data are believed to give a more reliable measure of the oxime produced.

Most variations in the preparative procedure given above resulted in lower yields of oxime; a few had no significant effect. Use of the calcium salt of nitrocyclohexane, which is largely insoluble in methanol, gave the same yield within the experimental error as the moderately soluble sodium salt. Substitution of the soluble potassium salt (the only salt tried which dissolves completely under the conditions of the experiment) resulted in yields only about two thirds as great. Diethyl sulfate appears to give slightly lower yields than dimethyl sulfate, but the difference may be within the experimental error. Diethyl sulfate does not react as rapidly as dimethyl sulfate. At room temperature or even at 0°, addition of dimethyl sulfate produces vigorous reaction with immediate evolution of heat; a slight delay in evolution of heat is observed on adding diethyl sulfate. Diethyl ether, ethylene glycol, and mixtures of these with methanol as solvents resulted in lower yields than those obtained in pure methanol; in water the yield was very low. Yields were not greatly changed by variation of the reaction temperature from 20° to the reflux temperature of the methanolic solution, but were considerably reduced at 0° and at 100°. Addition of the *aci*-nitro salt to the dialkyl sulfate gives lower yields than the reverse procedure. No increase in yield of the desired product was obtained by using other than stoichiometric amounts of reagents. An excess of alkyl sulfate results in formation of a significant amount of the corresponding alkyl ether of cyclohexanone oxime, rather than an increase in yield of oxime.

Other alkylations. The procedure used in reaction of salts of *aci*-nitrocyclohexane with alcohols and acid is similar to that of Welz and Weise,[2] but the ammonium salt was omitted

TABLE I

m/e	Cyclohexanone	Nitrocyclohexane (in Methanol)	Cyclohexanone Oxime (in Methanol)
129		0.	
114			8.6
113			100.-[a]
112			5.1
99	8.8	1.0	1.8
98	100.-[a]	0.8	27.
96	0.5		17.
85	0.3	0.4	19.
84	2.3	7.1	15.
83	20.	100.-[a]	2.7
82		10.	4.2
81	2.3	12.	28.
80	12.	0.6	6.4
79	1.9	3.6	10.
72	0.3	0.7	48.
70	52.	0.6	6.8
69	71.	1.5	17.
68	2.8	1.3	29.
67	1.0	15.	29.
59		1.7	54.
55	211.	128.	49.
54	15.	12.	28.
42	122.	5.9	28.
41	54.	77.	58.
39	32.	39.	30.
Sensitivity[b]	2.98	1.77	2.49

[a] Indicates the peak used as the basis for quantitative calculation of mixtures. [b] This value indicates the ratio of the *m/e* 92 peak of toluene to the base peak of the particular component on the weight basis; for example, 2.98 milligrams of cyclohexanone would give a *m/e* 98 peak of the same height as the *m/e* 92 peak of 1.00 milligram of toluene.

(8) The salt of *aci*-nitrocyclohexane could be detected by titrating back with acid, while nitrocyclohexane could be reconverted to the salt by stirring at high pH.

(9) Diazomethane or other alkylating agents might also be successful.

(10) An exhaustive search of the literature and considerable unpublished effort in the laboratory have failed to provide any evidence for other reaction paths involving organic reducing agents.

and the temperature was lowered in an attempt to detect the ester rather than the oxime. In reaction of alkyl halides with salts of nitrocyclohexane the procedure employed differs from the reference,[1] in that the salt was first prepared by shaking an equivalent amount of base with a methanolic solution of the nitroparaffin until reaction was complete. The alkyl halide was then added in stoichiometric quantity and the mixture was stirred for several hours while controlling the temperature with a bath of ice, Dry Ice, or other coolant around the vessel.

Titrations. The titrimetric experiments employed about 0.01 mole of nitrocyclohexane or its salt, dissolved or suspended in 50 ml. or more of solvent (methanol or ethanol; a few runs were also tried in water). 1 *N* HCl and NaOH were used as titrating reagents. A Leeds and Northrup electronic *p*H recording titrator was used.

Nitrocyclohexane does not interfere with titration. In methanolic media it does not react at an appreciable rate with base until the *p*H reading exceeds 11. Since hydrochloric acid makes little contribution to the titration curve above *p*H 3 in either water or methanol the bulk of the measured *p*H range is free of obstacles to titrating *aci*-nitrocyclohexane or its salt. The curves obtained in methanol are displaced toward higher *p*H than in water. Neither are symmetric because of the disappearance of the free *aci* form. Therefore the exact strength of *aci*-nitrocyclohexane is not readily determined from the titration curves. *Aci*-nitrocyclohexane appears to be comparable in strength to acetic acid—perhaps slightly stronger. This is similar to the reported ionization of *aci*-nitroethane.[11]

Mass spectrometer analysis. The mass spectrum of cyclohexanone dimethyl acetal, a frequent component of the reaction mixtures in this work, is presented elsewhere.[12] The mass spectra of the other important compounds involved in these reactions are shown in Table I. Peaks below *m/e* 35 were not used for analytical purposes and have been omitted here.

All analyses were performed on a modified 90° sector type mass spectrometer.[13] The sample inlet system temperature was 100° and the ion source temperature was 160°.

Calculation of the mass spectra of the samples was done by the usual stepwise subtraction of component spectra[14] in the conventional manner and needs no further explanation here.

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(11) Maron and Shedlovsky, *J. Am. Chem. Soc.*, **61**, 753 (1939).

(12) McCoy, Baker, and Gohlke, to be published.

(13) The instrument has been described by Caldecourt, ASTM Committee E-14 Mass Spectrometer Conference, New Orleans, May 1954.

(14) Washburn, Wiley, and Rock, *Ind. Eng. Chem., Anal. Ed.*, **15**, 541 (1943).

[Contribution from the Institute for Chemical Research, Kyoto University]

Nitration of Desoxybenzoin

MICHIYASU SUGII AND RISABURO NAKAI

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The action of nitric acid (*d* 1.30) on desoxybenzoin-carbonyl-C^{14} has been investigated. The reaction routes have been elucidated from radio assay of the reaction products and their fission products.

In the nitration of desoxybenzoin to nitrobenzil reported by Zinin,[1] it is not possible to decide which benzene nucleus of desoxybenzoin is nitrated. The nitration of the benzyl nucleus seems to be more probable, since Ney[2] found that desoxybenzoin gave *p*-nitrodesoxybenzoin by treating with fuming nitric acid at low temperatures. A decision as to the reaction route, however, is possible by using desoxybenzoin labeled in the carbonyl with isotopic carbon, since the different routes of reactions will lead to isotopically distinguishable products.

The syntheses and the reaction routes are shown in Fig. 1. The measured specific activities of the products at each step are also shown under the formulas. For the determination of specific radioactivity, the labeled compounds were burned in a wet combustion apparatus described by Claycomb *et al.*,[3] and converted to barium carbonate. The activity was counted at infinite thickness with a Geiger-Müller counter tube and compared with the count of a standard barium carbonate.

By the nitration of desoxybenzoin-carbonyl-C^{14} (I), prepared from phenylacetic acid-carboxyl-C^{14}, there were obtained benzoic acid-carboxyl-C^{14} (VI), inactive *p*-nitrobenzoic acid (V) and a mixture of *p*-nitrobenzil-carbonyl-C^{14} (II) and benzil-carbonyl-C^{14} (III). As the nitrating agent more concentrated nitric acid (*d* 1.30) than Zinin's nitric acid (*d* 1.20) was used, because the former gave better yield of pure II. The crude mixture of the two benzils was purified by means of chromatography

(1) N. Zinin, *Ann.*, Supplementbandes **3**, 154 (1864). The position of nitro group of nitrobenzil obtained by him was obscure and he reported that when nitrobenzil was treated with alcoholic potassium hydroxide, he obtained oxybenzoic acid and azobenzoic acid.

(2) E. Ney, *Ber.*, **21**, 2448 (1888).

(3) C. K. Claycomb, T. T. Hutchens, and J. T. Van Bruggen, *Nucleonics*, **7**, No. 3, 38 (1950).

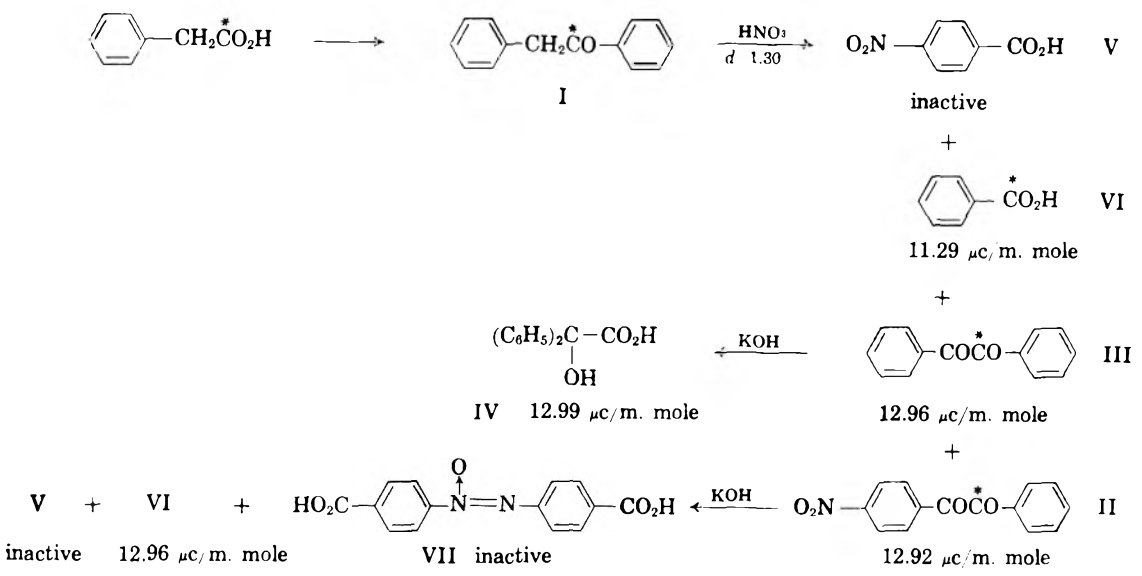

FIG. 1

and separated into each component, II and III, by fractional crystallization; compound II gave yellow minute scales, m.p. 141–142° and III gave yellow needles, m.p. 93–94°. Compound III was identified by conversion into benzilic acid-1-C^{14} or -2-C^{14} (IV).

When treated with alcoholic potassium hydroxide, II decomposed easily into inactive *p,p'*-azoxydibenzoic acid (VII), benzoic acid-carboxyl-C^{14} (VI) and inactive *p*-nitrobenzoic acid (V). The nitro derivatives of the decomposition products showed no activity and the specific activity of VI was equal to that of II. These facts indicate that in the nitration of I, the nitro group enters a *para* position to the methylene group of desoxybenzoin-carbonyl-C^{14}.

The nonlabeled specimens of *p*-nitrodesoxybenzoin, *p*-nitrobenzil, and benzil were synthesized and treated with the nitric acid, respectively, in the same manner as mentioned above. *p*-Nitrodesoxybenzoin gave benzoic acid, *p*-nitrobenzoic acid, and *p*-nitrobenzil. Benzil and *p*-nitrobenzil, however, were resistant to nitration and oxidation and were recovered quantitatively. These results would lead to the following conclusions. In the course of the action of the nitric acid on desoxybenzoin-carbonyl-C^{14}, the *p*-nitrodesoxybenzoin-carbonyl-C^{14} is formed as an intermediate product, and its methylene group is oxidized to a carbonyl group, and produces *p*-nitrobenzil-carbonyl-C^{14}. The oxidative disruption of the same intermediate, which occurs simultaneously with the above oxidation, gives benzoic acid-carboxyl-C^{14} and inactive *p*-nitrobenzoic acid. A similar oxidation prior to the nitration of desoxybenzoin-carbonyl-C^{14} also takes place and yields benzil-carbonyl-C^{14}, which undergoes no reaction with the nitric acid. On the other hand, oxidative disruption prior to nitration of desoxybenzoin-carbonyl-C^{14} will produce both inactive and active benzoic acid and cause some decrease in the specific activity of the isolated benzoic acid-carboxyl-C^{14}. This concept was confirmed by the fact that the specific activity of benzoic acid-carboxyl-C^{14}, which had been produced through the two reaction routes of desoxybenzoin-carbonyl-C^{14}, was comparatively lower (11.29 μc/mmol.) than the theoretical value (12.95 μc/mmol.) expected from the specific activity of starting material.

The essential reaction routes of the reaction of desoxybenzoin-carbonyl-C^{14} with nitric acid is shown in Fig. 2.

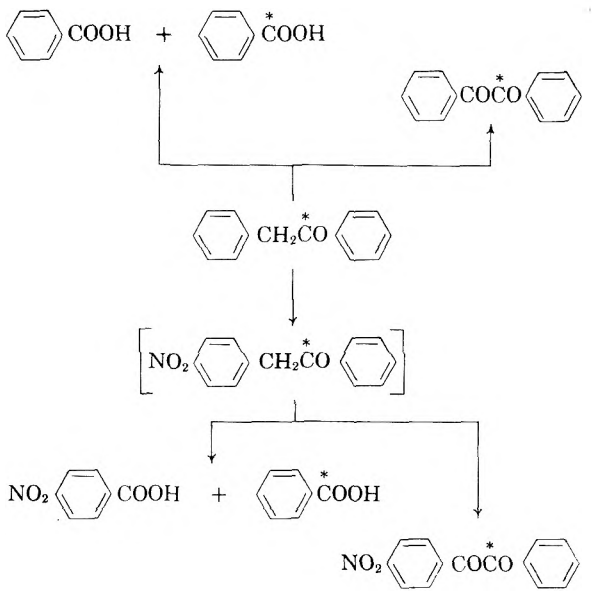

FIG. 2

EXPERIMENTAL

Desoxybenzoin-carbonyl-C^{14} (I). To 8.05 g. of phenylacetic acid-carboxyl-C^{14} (12.87 μc/m.mol.) in a 200 ml. two-neck flask fitted with a reflux condenser was added 15 g. of thionyl chloride. The mixture was heated on a water bath for 20

min. The thionyl chloride was removed under vacuum and after the residue was allowed to cool, 50 ml. of dry benzene and 9 g. of anhydrous aluminum chloride were added. The mixture was refluxed for 1 hr. on a water bath, then cooled, and poured onto a mixture of 100 g. of cracked ice and 5 ml. of concentrated hydrochloric acid. The benzene layer was separated, and the aqueous layer was extracted with a mixture of 25 ml. of benzene and 25 ml. of ether. The ether-benzene solution was washed with 20 ml. of water, and dried over calcium chloride. The solvent was removed under reduced pressure. The residue was recrystallized twice from methanol; yield, 6.95 g.; m.p. 54–55°. It had a specific activity of 12.95 μc per mmol. On further cooling of the mother liquor, 2.01 g. of crystals was obtained. The total yield of product was 8.96 g. (77.5%).

Nitration of desoxybenzoin-carbonyl-C^{14}. (a) *p-Nitrobenzil-carbonyl-C*^{14} (II). To 68 g. of nitric acid (*d* 1.30) was added 8.46 g. of I and the mixture was gently refluxed for 40 min. The cooled mixture was poured into 800 ml. of water and boiled. The heavy yellow oil was separated from the hot aqueous liquor by means of hot funnel. This oil layer solidified and 6 g. of yellow crystals was obtained, m.p. 60–80°. The benzene solution of crude crystals was passed through the alumina-column. The eluted residue was recrystallized thrice from ethanol. The final pure product formed yellow minute scales (m.p. 141–142°) and was obtained in a yield of 1.74 g. (15.8%). It had a specific activity of 12.92 μc per mmol.

Anal. Calcd. for $C_{14}H_9O_4N$: C, 65.88; H, 3.55; N, 5.49. Found: C, 66.10; H, 3.64; N, 5.32.

(b) *Benzil-carbonyl-C*^{14} (III). The mother liquor (ethanol) separated from II was evaporated and 3.87 g. of yellow residue was obtained. The residue was redissolved in 50 ml. of ethanol and allowed to stand overnight at room temperature. The long yellow needles were collected and weighed, 1.48 g. (16.4%), m.p. 89–94°. The benzene solution of crystals was passed through the alumina column. The eluted residue was recrystallized twice from ethanol and yielded 0.79 g. (8.75%) of yellow needles, m.p. 93–94°. No depression in melting point occurred, when mixed with an authentic sample of benzil. It had a specific activity of 12.96 μc per mmol.

(c) *Benzilic acid-1-C*^{14} *or-2-C*^{14} (IV). From 0.738 g. of III, 0.613 g. (76.6%) of crude benzilic acid (m.p. 146–148°) was prepared, by the method of Liebig.[4] The crude product was recrystallized twice from benzene and yielded 0.508 g. (63.5%) of fine needles; m.p. 149–150°. It had a specific activity of 12.99 μc per mmol. When mixed with an authentic sample of benzilic acid, no depression in melting point occurred.

(d) *p-Nitrobenzoic acid* (V). The hot aqueous liquor described in (a), from which the yellow oil layer was separated, was allowed to stand overnight. The pale yellow crystals which were filtered and dried, weighed 1.49 g. (20.8%); m.p. 190–200°: The product was recrystallized five times from boiling water, and sublimed at a temperature of 140–150° and a pressure of 7 mm. The sublimate, when recrystallized from boiling water, yielded 0.3 g. (4.15%) of pale yellow scales, m.p. 238–239°. When mixed with an authentic sample of *p*-nitrobenzoic acid, no depression in melting point occurred. A 2.855 mg. sample contained an activity indistinguishable from the background.

(e) *Benzoic acid-carboxyl-C*^{14} (VI). The aqueous filtrate separated from crude V, described in (d) was combined with the mother liquor of V and the mixed aqueous solution was extracted with ether. After washing the ether solution with water, the ether was distilled off. The residue was sublimed at a temperature of 60–65° and a pressure of 7 mm. It formed almost white needles; m.p. 115–119°; yield, 0.916 g. (17.4%). After three sublimations, white needles, m.p. 120–121°, were obtained; yield, 0.765 g. (14.5%). It had a specific activity of 11.29 μc per mmol. When mixed with an authentic sample of benzoic acid, no depression in melting point occurred.

Decomposition of p-nitrobenzil-carbonyl-C^{14}. (a) *p,p'-Azoxydibenzoic-acid* (VII). To a solution of 1.7 g. of potassium hydroxide in a mixture of 7 ml. of water and 10 ml. of ethanol was added 1.66 g. of II and the mixture was refluxed for 20 min. on a water bath. After cooling, the precipitated crystalline product (potassium salt of VII) was filtered and washed with ethanol. The crystals were redissolved in 80 ml. of hot water and filtered. The filtrate was acidified with dilute hydrochloric acid. The gelatinous substance was precipitated, centrifuged and washed well with hot water. The yield was 0.784 g. (42%). This product was further boiled with ethanol, filtered, washed with hot ethanol, dissolved in dilute ammonia, and then reprecipitated with dilute hydrochloric acid. Reprecipitation was repeated five times to remove the other adsorbed radioactive compounds. The yield was 0.641 g. (34.3%). The purified product was a yellow, amorphous powder, insoluble in all solvents and did not melt below 300°. Its analytical data corresponded to *p,p'*-azoxydibenzoic acid, and the ultraviolet absorption spectrum was also identical with that of the authentic specimen.[5] A 2.585 mg. sample contained an activity indistinguishable from the background. λ_{max} 262 mμ (0.1*N* NaOH) log ϵ 4.06; 335 mμ, log ϵ 4.24.

Anal. Calcd. for $C_{14}H_{10}N_2O_5$: C, 58.74; H, 3.51; N, 9.79. Found: C, 58.52; H, 3.51; N, 9.73.

(b) *Benzoic acid-carboxyl-C*^{14} (VI). The filtrate separated from the potassium salt of VII was treated with 5 ml. of water and acidified with hydrochloric acid. After evaporating the solvent (ethanol), the residual aqueous solution was allowed to stand overnight at room temperature. The crystalline product was filtered, washed with 4 ml. of water, and sublimed at a temperature of 60–65° and a pressure of 7 mm. Almost colorless needles, m.p. 114–118°, were obtained; yield, 0.566 g. (71%). After three sublimations white needles, m.p. 120–121°, were obtained; yield, 0.406 g. (51%). It had a specific activity of 12.96 μc per mmol. When mixed with an authentic sample of benzoic acid, no depression in melting point occurred.

(c) *p-Nitrobenzoic acid* (V). The residual part from sublimation of VI was further sublimed at a temperature of 140–50° and a pressure of 7 mm. Yellow needles were obtained; yield, 0.145 g. (13.3%); m.p. 192–200°. The sublimate was recrystallized thrice from boiling water and pale yellow scales were obtained, yield 0.046 g. (4.2%), m.p. 238–239°. When mixed with an authentic sample of *p*-nitrobenzoic acid, no depression in melting point occurred. A 1.633 mg. sample contained an activity indistinguishable from the background.

Action of nitric acid on p-nitrodesoxybenzoin. To 30 g. of nitric acid (*d* 1.30) was added 4.0 g. of *p*-nitrodesoxybenzoin which was prepared from *p*-nitrophenylacetic acid by the method of Petrenko-Kritschenko.[6] The mixture was treated in the same manner as that described in the nitration of desoxybenzoin-carbonyl-C^{14} and gave 2.03 g. (47.7%) of *p*-nitrobenzil, 0.39 g. (14.0%) of *p*-nitrobenzoic acid, and 0.3 g. (14.7%) of benzoic acid.

Action of nitric acid on p-nitrobenzil and benzil. A mixture of 2 g. of *p*-nitrobenzil and 16 g. of nitric acid (*d* 1.30) and a mixture of 5 g. of benzil and 40 g. of nitric acid (*d* 1.30) were treated, respectively, in the same manner as described in the above. In these cases, no reaction was recognized. *p*-Nitrobenzil and benzil were recovered quantitatively; 1.99 g. (99.5%); 4.97 g. (99.5%).

TAKATSUKI, OSAKA-FU, JAPAN

(4) H. V. Liebig, *Ber.*, **41**, 1644 (1908).

(5) F. Meyer and K. Dahlem, *Ann.*, **326**, 334 (1903).

(6) P. Petrenko-Kritschenko, *Ber.*, **25**, 2242 (1892).

[CONTRIBUTION FROM THE PHARMACEUTICAL RESEARCH INSTITUTE, MEDICAL SCHOOL, KEIO-GIJUKU UNIVERSITY]

Santonin and Related Compounds. XI.[1] Bromination and Dehydrobromination of *cis*-9-Methyl-3-decalone[2]

MASAITI YANAGITA AND KOJI YAMAKAWA

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The usual treatment of *cis*-9-methyl-3-decalone (Ia) with bromine gave, unexpectedly, a 2-bromo compound in which the position of bromine was definitely established. This is not in accordance with the general rule about bromination of 3-ketosteroids. The 2-bromo and 2,4-dibromo compounds of the *cis*-ketone (Ia) were reacted with a variety of bases to give products of different type depending on the reagent used. The stereochemistry of 9-methyl-*cis*-3-decalols (XVII and XVIII) is discussed.

In the previous papers of this series,[3-5] bromine treatment of *trans*-9-methyl-3-decalone (Ib) was described as giving 2-bromo (IIb) and 2,4-dibromo derivatives (XIVb), which were reacted with various bases and converted to different products. Thus, the monobromo ketone with γ-collidine afforded the Δ^4-3-ketone (III), the rearranged product, while on acetolysis and with the Mattox-Kendall procedure it gave, respectively, the 2-acetoxy ketone (VIb) and the Δ^1-3-ketone (Vb), both the normal products. With γ-collidine or anhydrous sodium acetate, the 2,4-dibromo ketone was converted, respectively, to the $\Delta^{4(10),5(6)}$-dienone or the 2-acetoxy-Δ^1-3-ketone (XVIb), both the rearranged products. The present research was initiated to compare these bromination-dehydrobromination reactions of the *trans*-ketone (Ib) with those of the isomeric *cis*-ketone (Ia).

cis-9-Methyl-3-decalone was prepared by catalytic hydrogenation of the Δ^4-3-ketone (III), essentially as reported previously[6,7] (see Experimental section). The Δ^4-3-ketone was hitherto obtained by the condensation of 2-methylcyclohexan-1-one with 1-diethylamino-3-butanone methiodide in the presence of sodium amide in organic solvent, following the method first reported by duFeu, McQuillin, and Robinson,[7] or by a slight modification thereof. It was found now that when the free Mannich base instead of its methiodide was used with sodium metal in the absence of a solvent, the Δ^4-3-ketone of sufficient purity was obtained in a comparable yield. It provides a more economical and simple procedure for III than the earlier method.

The solid *cis*-ketone (Ia) was reacted with one mole of bromine to give an oily monobromo compound (IIa), which on treatment with γ-collidine, afforded the Δ^4-3-ketone (III) in a comparable yield with that from the *trans*-monobromo ketone (IIb).[3] By the Mattox-Kendall method, the monobromo ketone (IIa) was converted, in a good yield, to the *cis*-Δ^1-3-ketone 2,4-dinitrophenylhydrazone (IVa), showing $\lambda_{max}^{CHCl_3}$ 258 mμ (ε 15,000) and 362 mμ (ε 22,600). The hydrazone with pyruvic acid regenerated the known *cis*-Δ^1-3-ketone (Va), identified as the semicarbazone.[8] The location of the double bond in Va was proved by the ultraviolet absorption spectrum, λ_{max}^{EtOH} 229 mμ (ε 9500), corresponding to the α,β-unsaturated ketone with no substituents.[9]

On heating with anhydrous sodium acetate in glacial acetic acid, the monobromo ketone (IIa) was converted to an acetoxy ketone (VIa) in 80% yield. The acetoxy ketone with alkali afforded, together with the known *cis*-diacid (VIIa),[9] a 2,3-diketone (VIIIa) which gave a positive ferric chloride test (enol form; Xa, XIa, or both), and formed a glyoxime. Perhydrol oxidation of the acetoxyketone and the 2,3-diketone afforded good yields of the *cis*-diacid. As in the case of the *trans*-series (VIIb and VIIIb), these products are presumed to be formed from VIa *via* an intermediate α-ketol (IXa), commonly considered to be unstable. The results clearly indicated the location of the acetoxy group at the 2-position in VIa. The authentic sample of the *cis*-diacid (VIIa) was prepared, as reported previously,[9] by nitric acid oxidation of the *cis*-ketone (Ia), which was much more difficult than the similar oxidation of the *trans*-ketone (Ib).

The above reactions of the *cis*-monobromo ketone (IIa) with bases are completely in parallel with the corresponding reactions reported for the *trans*-isomer (IIb).[3] On analogy with the assignment of the 2-bromo structure (IIb) for the *trans*-monobromo ketone, it may be reasonably assumed that

(1) Paper X, Yanagita and Futaki, *J. Org. Chem.*, 21, 949 (1956).

(2) This work was supported in part by a grant in aid for Scientific Research from the Ministry of Education of Japan.

(3) Yanagita and Tahara, *J. Org. Chem.*, 18, 792 (1953).

(4) Yanagita, Yamakawa, Tahara, and Ogura, *J. Org. Chem.*, 20, 1767 (1955).

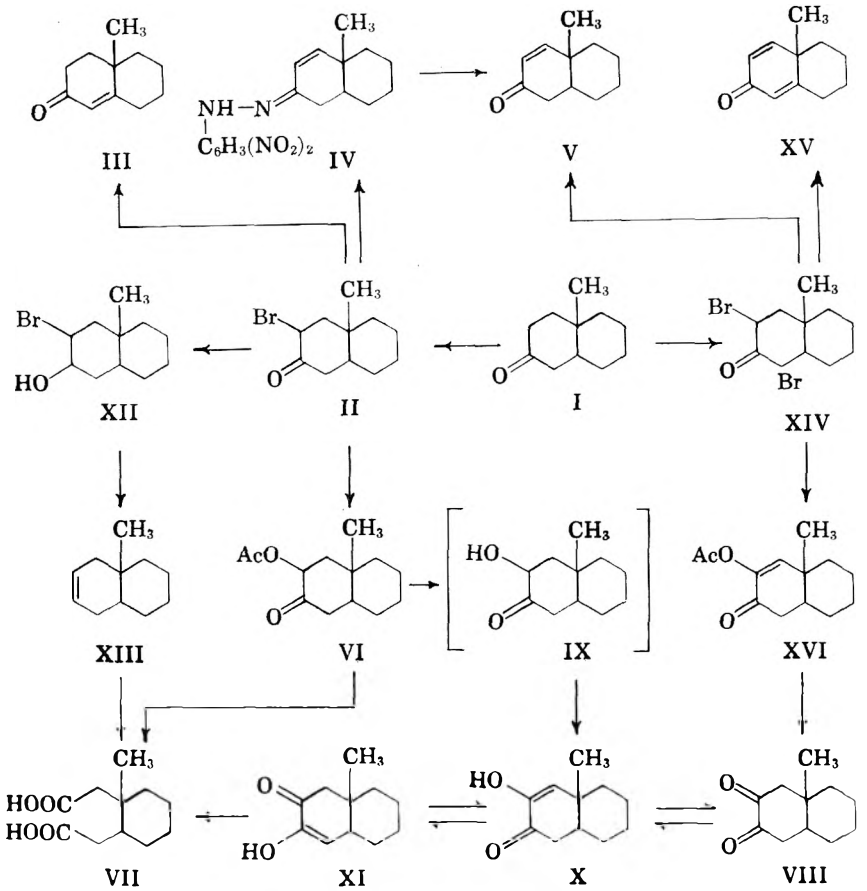
(5) Yanagita and Yamakawa, *J. Org. Chem.*, 21, 500 (1956).

(6) Woodward, Sondheimer, Taub, Heusler, and McLamore, *J. Am. Chem. Soc.*, 74, 4223 (1952).

(7) DuFeu, McQuillin, and Robinson, *J. Chem. Soc.*, 53 (1937): *cf.* Dauben, Rogan, and Blanz, Jr., *J. Am. Chem. Soc.*, 76, 6384 (1954).

(8) Burnop and Linstead, *J. Chem. Soc.*, 720 (1940).

(9) Fieser and Fieser, *Natural Products Related to Phenanthrene*, 3rd Ed., Reinhold Publishing Corp., New York, 1949, p. 190.



Series a, *cis*-configuration at the ring juncture
Series b, *trans*-configuration at the ring juncture

the *cis*-isomer also possesses the 2-bromo structure (IIa). It is desirable, however, to confirm this structure for the reason described below. The proof of the position of the bromine atom in IIa was obtained by using the same sequence of reactions (II → XII → XIII → VII) as that reported for IIb.[5] Sodium borohydride reduction of the *cis*-monobromo ketone (IIa) gave rise to a possible epimeric mixture of bromohydrins (XIIa). Without attempting to separate the epimers, the liquid product was treated with zinc dust and acetic acid to produce, together with the *cis*-ketone (Ia), an olefin (XIIIa), which exhibited a weak but sharp absorption band at 1655 cm.$^{-1}$, corresponding to a *cis*-disubstituted ethylene.[5] Contrary to the *trans*-olefin (XIIIb),[5] the *cis*-isomer is found to be quite resistant toward permanganate in acetone solution. Permanganate oxidation of this olefin was carried out with comparable ease in sodium carbonate solution to afford the *cis*-diacid (VIIa), giving conclusive evidence for the 2-bromo structure (IIa).

The above observation that substitution of bromine in the *cis*-3-decalone ring occurs preferentially at the 2- position seems remarkable, since it is not in accord with the general conclusion concerning bromination of 3-ketosteroids, in which the normal series (A/B rings *cis*) always affords the 4-bromo product whereas the allo series gives the 2-bromo compound.[10] If the theory that, on bromination of ketones, bromine first adds to the double bond of the enolic form of the ketones,[11,12] is applied to the present case, it may be seen that in *cis*-9-methyl-3-decalone (Ia), the Δ^2-enol is more favorable than the Δ^3-enol. This deduction is the reverse of the argument suggested by Taylor[13] that *cis*-Δ^1-octalin is more stable than the *cis*-Δ^2-octalin as observed with the enolic forms of the 3-ketosteroids of normal series.

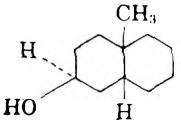
Treatment of the *cis*-ketone (Ia) with two moles of bromine gave a dibromo compound (XIVa), which was isolated in a liquid or a solid form depending on the temperature at which the reaction took place. The former was used for reaction with bases described below, and the latter, showing rather different chemical properties, will be reported in a separate paper.

(10) Shoppee and Shoppee in Rodd's *Chemistry of Carbon Compounds*, Elsevier Publishing Co., New York-Amsterdam, 1953, Vol. II, Part B, p. 832.
(11) Wheland, *Advanced Organic Chemistry*, 2nd Ed., John Wiley & Sons, Inc., New York, 1949, p. 587.
(12) Strain in Gilman's *Organic Chemistry, an Advanced Treatise*, 1st Ed., John Wiley & Sons, Inc., New York, 1938, p. 1273.
(13) Taylor, *Chemistry & Industry*, 250 (1954).

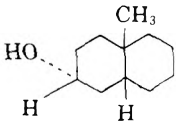
It was reported by Gunstone and Heggie[14] that dibromination-dehydrobromination (γ-collidine) of 9-methyl-3-decalone (I) gave rise to a low yield of the cross-conjugated dienone (XV), which was not isolated as a solid derivative but was converted in low yield to the tetralol by dienone-phenol rearrangement. Their starting material (I), prepared from the Δ^4-3-ketone (III) by catalytic hydrogenation, was apparently a mixture of stereoisomeric ketones,[6] as considered by these authors. From the earlier observation[3] that the 2,4-dibromo derivative (XIVb) of the *trans*-ketone (Ib) on collidine treatment afforded only the linearly conjugated dienone, it may be predicted that a similar treatment of the pure *cis*-dibromo ketone (XIVa) will lead to the cross-conjugated dienone (XV). This prediction was confirmed, but the product (XV) of poor purity was obtained only in a low yield, and was characterized as the 2,4-dinitrophenylhydrazone. It is notable that, in addition to the dienone, the Δ^1-3-ketone (Va) as lower-boiling fraction was isolated also in a low yield. As described above, this monoenone was not detected in the reaction of the *cis*-monobromo ketone (IIa) with hot collidine.

Reaction of the *cis*-2,4-dibromo ketone (XIVa) with anhydrous sodium acetate in glacial acetic acid proceeded similarly to that reported for the *trans*-isomer (XIVb),[2] and gave the 2-acetoxy-Δ^1-3-ketone (XVIa) and the above 2,3-diketone (VIIIa). The former product showed the ultraviolet absorption spectrum, λ_{max}^{MeOH} 239 mμ (ϵ 2300), corresponding to the Δ^1-enol acetate (XVIa) rather than the Δ^4-enol acetate (the acetate of XIa).[15] The 2-acetoxy-Δ^1-3-ketone was readily converted with alkali to the 2,3-diketone (VIIIa) and the diacid (VIIa), giving conclusive evidence for the structure (XVIa). From the foregoing results of reaction with bases, the *cis*-dibromo ketone may possibly be assigned the 2,4-dibromo structure (XIVa). However, the possibility that this dibromo ketone possesses the 2,2-dibromo structure cannot be completely ruled out, in view of the reported rearrangement of 6-bromo-2,4,4-trimethyl-Δ^5-cyclohexen-1-one to the cross-conjugated dienone.[16]

During this investigation, a search was made for preparing the stereoisomers of 9-methyl-*cis*-3-decalol. Hussey, Liao, and Baker[17] claimed that *trans*-9-methyl-*cis*-3-decalol (XVIII)[18] was obtained in a low yield (32%) by the hydrogenation of *cis*-9-methyl-3-decalone (Ia) over platinum dioxide under slight pressure. The evidence for this configurational assignment was based on the non-identity with "*cis*-9-methyl-*cis*-3-decalol" reported by these authors. However, since the latter decalol was shown to be *trans*-fused,[19] this argument is invalid and the configuration of the hydroxyl group in the hydrogenation product still remains unknown.



XVII



XVIII

It was found that *cis*-9-methyl-3-decalone (Ia) was quite resistant to hydrogenation with platinum dioxide at ordinary temperature and pressure. Lithium aluminum hydride reduction of the *cis*-ketone gave a quantitative yield of a solid alcohol, which is presumed to be identical with the compound obtained by Hussey, Liao, and Baker,[17] from the identity of the melting points of the alcohol itself and its derivatives, and from their method of preparation.

Reduction of the *cis*-ketone (Ia) with sodium and ethanol, which proceeded much less readily than that of the *trans*-ketone (Ib),[5] gave an oily alcohol in low yield. The use of amyl alcohol in place of ethanol markedly improved the results. Of the derivatives from this oil and the customary alcohol reagents, only a 3,5-dinitrobenzoate—α-naphthylamine complex and an anthraquinone-β-carboxylate were obtained crystalline. These derivatives were different from the corresponding derivatives of the solid alcohol. From the mode of their formations, we tentatively assign to the solid and liquid alcohols, respectively, the *cis*- and *trans*-configurations of hydroxyl-to-methyl group (XVII and XVIII), in which the hydroxyl group in the latter is more equatorial.[20] The use of the infrared absorption spectra (Fig. 1) for the elucidation of the configuration of these 9-methyl-3-decalols was unfruitful. Neither the C—O frequencies nor the structure of the 1240 cm.$^{-1}$ acetate band, which are known to serve for configurational assignment of the hydroxyl group in 3-decalols with no angular methyl groups and analogous steroids,[21] gave any insight into the configuration of the hydroxyl group in our alcohols.

In conclusion, we should like to describe the relative reactivities of some pairs of the *cis*- and *trans*-series of the compounds cited above. Previously, it was reported[22] that on reaction with a stereoisomeric mixture of 4,9-dimethyl-3-decalones,

(14) Gunstone and Heggie, *J. Chem. Soc.*, 1437 (1952).
(15) Reference 9, p. 195.
(16) Yanagita and Inayama, *J. Org. Chem.*, 19, 1724 (1954).
(17) Hussey, Liao, and Baker, *J. Am. Chem. Soc.*, 75, 4727 (1953).
(18) For an explanation of this nomenclature, see footnote 3 in reference 18.
(19) Dauben, Tweit, and MacLean, *J. Am. Chem. Soc.*, 77, 48 (1955): Dreiding and Tomasewski, *J. Am. Chem. Soc.*, 77, 168 (1955).
(20) Dauben, Tweit, and Mannerskantz, *J. Am. Chem. Soc.*, 76, 4420 (1954).
(21) Braude and Waight in Klyne's *Progress in Stereochemistry*, Academic Press Inc., New York, 1954, Vol. I, p. 166.
(22) Yanagita and Futaki, *J. Org. Chem.*, 21, 949 (1956).

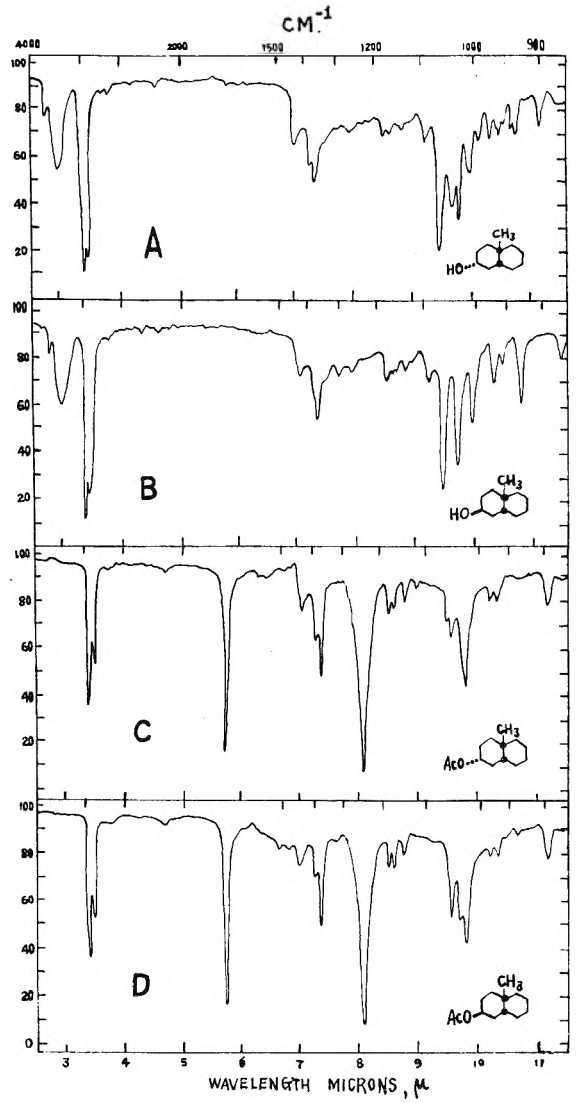


FIG. 1.—INFRARED ABSORPTION SPECTRA (in Carbon Disulfide Solution): A, *trans*-9-Methyl-*cis*-3-Decalol (XVIII); B, *cis*-9-Methyl-*cis*-3-Decalol (XVII); C, the Acetate of XVIII; D, the Acetate of XVII.

diethyl oxalate selectively attacked one isomer with a *trans*-configuration at the ring juncture. Similar stereospecificity was observed, as shown above, in nitric acid oxidation and sodium-alcohol reduction of 9-methyl-3-decalones (Ia and Ib) and in permanganate oxidation of 9-methyl-Δ^2-octalins (XIIIa and XIIIb), in which the *trans*- isomer is always more reactive than the *cis*- isomer.

EXPERIMENTAL[23]

3-Keto-9-methyl-Δ^4-octahydronaphthalene (III). This was prepared by an effective variation of the method reported first by duFeu, McQuillin, and Robinson.[7] To a solution of 5.3 g. of 2-methylcyclohexan-1-one and 2.5 g. of 1-diethylaminobutan-3-one[24] in the presence of a small amount of hydroquinone was added, in small pieces, 0.1 g. of sodium metal at room temperature. After the sodium dissolved, the mixture was slowly heated to 135° in an oil bath, and this temperature was maintained for 3 hr. The dark brown solution was cautiously acidified with 10% hydrochloric acid under ice-cooling, and extracted with ether. Washing with water, drying, and evaporation of the ether extract gave an oily residue, which was distilled to give, with a considerable forerun (b.p. 65–70° at 30 mm.) containing the starting material, 1.0 g. (35%) of the Δ^4-3-ketone (III), b.p. 102–110° at 2.5 mm. Reported, b.p. 139° at 15 mm.[7]

It formed, in almost quantitative yield, the 2,4-dinitrophenylhydrazone, m.p. 145–150°, which was recrystallized from ethanol to give scarlet plates, m.p. 169°. Reported, m.p. 169°.[7]

Use of 1-N-piperidinobutan-3-one[25] instead of 1-N-diethylaminobutan-3-one gave almost the same result. To a mixture of 10.0 g. of N-piperidinobutanone, 15.0 g. of 2-methylcyclohexanone, and a small amount of hydroquinone, 0.3 g. of sodium metal was added with ice-cooling. The mixture was treated as described above and 3.5 g. (32%) of the Δ^4-3-ketone (III), b.p. 110–120° at 4 mm., was obtained, with recovery of 12.0 g. of the starting materials.

cis-9-Methyl-3-decalone (Ia). This was prepared by catalytic hydrogenation of the above monoenone (III) in the presence of palladium chloride, essentially following the method reported previously.[6,7] The procedure for isolation of the *cis*-ketone (Ia) from the hydrogenation mixture of isomeric ketones was improved. The monoenone (III, 10.0 g.), b.p. 140–150° at 16 mm., was hydrogenated over palladium-charcoal (prepared from 20 cc. of 1% palladium chloride solution and 2.0 g. of charcoal) at ordinary temperature and pressure. In 40 min., 1290 cc. (0.95 mole) of hydrogen was absorbed. After removal of the catalyst and solvent, the residual oil was subjected to steam-distillation. The first distillate (250 cc.) gave a colorless oil which immediately solidified. Filtering, drying, and washing with petroleum ether afforded 5.75 g. (57%) of *cis*-9-methyl-3-decalone (Ia), white prisms, m.p. 46°. An oil from the second distillate (100 cc.) was fractionated to give 3.45 g. of a colorless oil, b.p. 113–128° at 10 mm., which partly solidified on being stored in a refrigerator. Filtering by suction and washing with cold petroleum ether gave an additional 1.40 g. (total 70%) of the *cis*-ketone (Ia), m.p. 47°. Reported, m.p. 46–48°[6] and m.p. 47°.[7] It formed quantitatively the 2,4-dinitrophenylhydrazone, m.p. 152°, which was refluxed in ethanol for several hours and then recrystallized from ethanol to give orange needles, m.p. 173°. Reported, m.p. 174.5–175.5°.[6] The semicarbazone, m.p. 168–175°, obtained in 90% yield, was recrystallized from ethanol to give colorless prisms, m.p. 198–201°. Reported, m.p. 201–202°.[6] A colorless viscous oil,[26] separated from the solid ketone (Ia), amounted to 2.05 g. (20%).

cis-2-Bromo-9-methyl-3-decalone (IIa). To a stirred solution of 2.0 g. of *cis*-9-methyl-3-decalone (Ia), m.p. 46°, in 25 cc. of chloroform was added, dropwise, a solution of 2.0 g. of bromine in 15 cc. of the same solvent under ice-cooling. Bromine was immediately absorbed, and after the addition was completed, the stirring was continued for an additional 40 min. at room temperature. Evaporation of the chloroform under reduced pressure left a yellow oil, which was distilled to yield 2.7 g. (92%) of a pale yellow oil, b.p. 130–144° at 4 mm. When the bromination of Ia was carried out in glacial acetic acid, as described for preparing the *trans*-

(23) All temperatures are uncorrected. Infrared absorption spectra were determined with a Perkin-Elmer model 21 double-beam spectrophotometer by Mr. Shindo of the Sankyo Co. Ltd., Tokyo, to whom the authors are greatly indebted. Microanalyses were by Miss Shibuya, and ultraviolet measurement by Miss Suzuki, both of this School.

(24) Wilds and Shunk, *J. Am. Chem. Soc.*, 65, 469 (1943).

(25) Wilds and Werth, *J. Org. Chem.*, 17, 1149 (1952).

(26) Further separation of this mixture was effected through the hydroxymethylene derivative which will be reported in the near future.

monobromo ketone (IIb) from Ib,[3,5] the yield of IIa was relatively low (67%).

Reaction of cis-2-bromo-9-methyl-3-decalone (IIa) *with γ-collidine.* A solution of 0.39 g. of the above monobromo ketone (IIa) in 1 cc. of γ-collidine (b.p. 169–170°) was heated to a gentle reflux for 10 min. On cooling, the dark brown mixture was diluted with ether, and the collidine hydrobromide (0.31 g., 96%) was filtered off. The ether solution was worked up in the usual manner.[16] There was obtained 0.11 g. (42%) of a colorless oil, b.p. 103–124° at 4 mm.; λ_{max}^{MeOH} 236 mμ (ε 10,000), chiefly consisting of the Δ⁴-3-ketone (III). This fraction formed, in 86% yield, the 2,4-dinitrophenylhydrazone, melting in the range of 98–121°, which was recrystallized from ethanol to give scarlet plates, m.p. 169°, undepressed on admixture with the sample described above.

Mattox-Kendall reaction of cis-2-bromo-9-methyl-3-decalone (IIa). To a solution of 0.10 g. of the *cis*-monobromo ketone (IIa) in 2 cc. of acetic acid was added 0.10 g. of 2,4-dinitrophenylhydrazine and the mixture was heated on a water bath for 5 min. After standing at room temperature for 2 hr., the reaction mixture was poured onto water (5 cc.), and 3-keto-9-methyl-Δ¹-octahydronaphthalene 2,4-dinitrophenylhydrazone (IVa) (0.13 g., 93%) was collected by filtration. Three recrystallizations from ethanol gave red needles, m.p. 153°; $\lambda_{max}^{CHCl_3}$ 258 mμ (ε 15,000) and 362.5 mμ (ε 22,600). On admixture with the same derivatives of the Δ⁴-3-ketone (III) and the *trans*-isomer (IVb), m.p. 161–162°,[5] the melting points were depressed to 124–132° and 127–131°, respectively.

Anal. Calcd. for $C_{17}H_{20}N_4O_4$: C, 59.29; H, 5.85; N, 16.27. Found: C, 58.97; H, 6.05; N, 16.75.

To a suspension of 0.15 g. of the above hydrazone derivative (IVa) in 10 cc. of 50% acetic acid was added 0.5 cc. of freshly prepared pyruvic acid and the mixture was heated for 2 hr. on a water bath. On cooling, the clear yellow solution, separating yellow crystals, was neutralized with anhydrous sodium carbonate and extracted with ether. Washing with 10% aqueous sodium hydroxide, drying, and evaporation of the ether extract yielded a light brown oil, which was fractionated to 0.05 g. (63%) of the *cis*-Δ¹-3-ketone (Va), as a colorless oil, b.p. 95–96° at 3 mm.; λ_{max}^{EtOH} 229 mμ (ε 9500).

Anal. Calcd. for $C_{11}H_{16}O$: C, 80.44; H, 9.83. Found: C, 80.43; H, 9.81.

It formed quantitatively the semicarbazone, m.p. 200–201° (after recrystallization from dilute ethanol). Reported, m.p. 200–201°.[8]

Anal. Calcd. for $C_{12}H_{19}N_3O$: N, 18.99. Found: N, 19.00.

Reaction of cis-2-bromo-9-methyl-3-decalone (IIa) *with unhydrous sodium acetate. cis-2-Acetoxy-9-methyl-3-decalone* (VIa). A mixture of 0.51 g. of the *cis*-monobromo ketone (IIa) and 0.46 g. of anhydrous sodium acetate in 3.8 cc. of glacial acetic acid was refluxed in an oil bath for 2 hr. with exclusion of moisture. After cooling, the reaction mixture was poured onto 20 cc. of water and worked up as described for the *trans*-monobromo ketone (IIb).[3] As an alkali-soluble product, a minute amount of an oil, showing a violet-brown coloration with ferric chloride, was obtained. Presumably this oil contains the 2,3-diketone (VIIIa) described below, but it could not be characterized as a solid derivative. The oily neutral product was distilled to give 0.375 g. (80%) of *cis*-2-acetoxy ketone (VIa) as a colorless oil, b.p. 120–135° at 5 mm. Redistillation afforded an analytical sample, b.p. 125–130° at 4 mm.

Anal. Calcd. for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 70.03; H, 9.02.

Reaction of cis-2-acetoxy-9-methyl-3-decalone (VIa) *with alkali.* The above 2-acetoxy ketone (VIa) was treated with alkali under conditions similar to those reported for the *trans*-isomer (VIb).[3] The *cis*-acetoxy ketone (VIa, 1.0 g.) was added to 17 cc. of 6% methanolic potassium hydroxide solution with cooling, and the mixture was allowed to stand at room temperature for 48 hr. A pale yellow solution was evaporated under reduced pressure, the residue was mixed with a small amount of water, and extracted with ether. Evaporation of the dried ether solution yielded 0.14 g. (14%) of an oil, containing mainly the starting acetoxy ketone.

The alkali solution was acidified and extracted with ether, and the ether solution was shaken with saturated sodium bicarbonate and with water, and dried. Evaporation of the ether left a yellow oil (0.42 g.) which was distilled to give 0.27 g. (33.5%) of *cis-2,3-diketo-9-methyldecalin* (VIIIa), a colorless oil, b.p. 115–116° at 4.5 mm.; λ_{max}^{EtOH} 271 mμ (ε 6500). It gave blue-violet coloration with ferric chloride. This formed, in 86% yield, a *glyoxime*, melting in the range of 170–180°, which was recrystallized from ethanol to give colorless prisms, m.p. 200–201° (dec.), showing red coloration with nickel salt.

Anal. Calcd. for $C_{11}H_{18}N_2O_2$: C, 62.83; H, 8.63; N, 13.32. Found: C, 62.94; H, 8.37; N, 13.23.

The above bicarbonate solution was acidified and extracted with ether. Evaporation of the ether gave 0.32 g. of an oil which mostly solidified. Two recrystallizations from ethyl acetate afforded colorless prisms, m.p. 189–190°, undepressed on admixture with *cis*-1-methylcyclohexane-1,2-diacetic acid (VIIa) described below.

Oxidation of cis-2-acetoxy-9-methyl-3-decalone (VIa) *and cis-2,3-diketo-9-methyldecaline* (VIIIa) *with Perhydrol.* The *cis*-acetoxy ketone (VIa) was oxidized with Perhydrol (H_2O_2) by the procedure similar to that reported for the *trans*- isomer (VIb).[3] To a solution of 0.08 g. of VIa in 2 cc. of 6% methanolic potassium hydroxide was added dropwise 0.4 cc. of 30% Perhydrol. The mixture, which became turbid, was allowed to stand overnight at room temperature. The clear solution was worked up as usual, and there was obtained 65 mg. (85%) of the *cis*-diacid (VIIa), m.p. 170–178°, which was recrystallized from ethyl acetate to give colorless prisms, m.p. and mixed m.p. 188–190°.

The *cis*-2,3-diketone (VIIIa, 35 mg.) was treated with 0.2 cc. of Perhydrol in 1 cc. of methanolic potassium hydroxide solution as described above, but the mixture was allowed to stand for 6 hr. The crude *cis*-diacid, isolated in 90% yield, was recrystallized from ethyl acetate to give colorless prisms, m.p. and mixed m.p. 189–190°.

cis- and trans-1-Methylcyclohexane-1,2-diacetic acids (VIIa and VIIb, respectively). The *cis*-diacid (VIIa) was prepared by a slight modification of the method reported by Linstead, Millidge, and Walpole.[27] A mixture of 0.30 g. of the *cis*-ketone (Ia) and 4 cc. of concentrated nitric acid was heated to reflux for 30 min. After cooling, water (1.5 cc.) was added and the mixture was refluxed for one additional hour. On standing in a refrigerator overnight, 0.15 g. (40%) of the *cis*-diacid (VIIa) precipitated as a colorless solid, m.p. 160–170°. Recrystallization from ethyl acetate gave colorless prisms, m.p. 189–190°. Reported, m.p. 189–190°[10] and m.p. 190–191°.[28]

Anal. Calcd. for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.61; H, 8.81.

The optically active *trans*-diacid was reported to have been prepared from 1-*trans*-9-methyl-3-decalone by nitric acid oxidation.[29] The optically inactive *trans*-diacid was obtained from Ib by a slight modification of the reported procedure. The *trans*-ketone (Ib, 0.30 g.) was added dropwise to 4 cc. of concentrated nitric acid (*d* 1.44) under shaking. Slightly exothermic reaction took place under violent evolution of a brown-red gas. On refluxing the

(27) Linstead, Millidge, and Walpole, *J. Chem. Soc.*, 1140 (1937).

(28) Dreiding and Tomasewski, *J. Org. Chem.*, 19, 241 (1954).

(29) Gautschi, Jeger, Prelog, and Woodward, *Helv. Chim. Acta*, 38, 296 (1955); Riniker, Kalvoda, Arigoni, Fürst, Jeger, Gold, and Woodward, *J. Am. Chem. Soc.*, 76, 313 (1954).

mixture in an oil bath for 3 min., the violent reaction subsided. (Under such conditions, oxidation of the *cis*-ketone did not begin.) After addition of 1.5 cc. of water, the mixture was refluxed for further 30 min. There was obtained the *trans*-diacid (0.25 g., 65%), m.p. 190–193°, which was recrystallized from ethyl acetate to give crystals, m.p. 193–195°. Reported, m.p. 195°.[30]

Sodium borohydride reduction of cis-2-bromo-9-methyl-3-decalone (IIa).[31] The *cis*-monobromo ketone (IIa, 1.23 g.) was reduced with 0.20 g. of sodium borohydride in methanol as described for the *trans*-isomer (IIb).[5] The oily product (1.18 g.) was distilled to give a colorless viscous oil (0.95 g.), b.p. 116–123° at 3 mm., which presumably consisted predominantly of epimers of 2-bromo-9-methyl-*cis*-3-decalol (XIIa). It formed no precipitate with Brady's reagent (an alcoholic solution of 2,4-dinitrophenylhydrazine and sulfuric acid).

Zinc reduction of 2-bromo-9-methyl-cis-3-decalol (XIIa).[31] By the procedure reported for the *trans*-bromohydrin (XIIb),[5] 0.95 g. of the *cis*-isomer (XIIa) was reduced with 8.0 g. of zinc dust in 40 cc. of glacial acetic acid. The product, a pale yellow oil (0.62 g.), was distilled giving two fractions; a colorless oil (0.33 g., 57%), b.p. 108–115° at 50 mm., and a colorless oil (0.19 g., 30%), b.p. 121–125° at 12 mm. The lower-boiling fraction, which contained predominantly 9-methyl-Δ^2-octalin (XIIIa), was redistilled to give an oil, b.p. 107–109° at 48 mm. The infrared absorption spectrum possesses a weak but sharp band at 1653 cm.$^{-1}$, corresponding to a *cis*-disubstituted ethylene,[5] and a weak carbonyl band at 1718 cm.$^{-1}$, indicative of contamination with a trace amount of Ia. The higher-boiling fraction gave the crystalline *cis*-ketone (Ia), m.p. and mixed m.p. 48° (after washing with petroleum ether).

Permanganate oxidation of cis-9-methyl-Δ^2-octalin (XIIIa). In contrast to *trans*-9-methyl-Δ^2-octalin (XIIIb),[5] the *cis*-isomer (XIIIa) is quite resistant to permanganate in acetone solution at room temperature. The oxidation was effectively carried out with permanganate in sodium carbonate solution, essentially by the procedure reported previously.[32] To a mixture of 0.10 g. of the *cis*-octalin (XIIIa), 5 cc. of water, and a drop of 5% sodium carbonate, 25 cc. of 1% aqueous potassium permanganate solution was added dropwise under rapid stirring. The addition was completed in 3 hr. The reaction mixture was treated with sulfur dioxide and the separated oil solidified on standing in a refrigerator. The crystals (35 mg., 25%), m.p. 180°, were recrystallized from water to give white nodules, m.p. 189–190°, undepressed on admixture with the *cis*-diacid (VIIa) above described. The mother liquor of the crystals gave an additional 10 mg. (total 32%) of the *cis*-diacid (VIIa).

Dibromination-dehydrobromination of cis-9-methyl-3-decalone (Ia). The *cis*-ketone (Ia, 0.60 g.) was brominated with 2 moles of bromine, and the product, without purification, was heated with γ-collidine (3 cc.) at 170° for 70 min., by the procedure reported by Gunstone and Heggie[14] for the 9-methyl-3-decalone (I). Distillation of the oily product afforded a pale yellow oil (120 mg., 20.5%), boiling in the range 98–180° at 3 mm.; λ_{max}^{EtOH} 246 mμ (ϵ 8100). Redistillation gave two fractions; a colorless oil (0.03 g., 5%), b.p. 95–110° at 3 mm.; λ_{max}^{EtOH} 234 mμ (ϵ 8000), and a pale yellow oil (0.04 g., 7%), b.p. 130–140° at 3 mm.; λ_{max}^{EtOH} 240 mμ (ϵ 6000). The lower-boiling fraction formed, in 81% yield, the Δ^1-3-ketone 2,4-dinitrophenylhydrazone (IVa), m.p. 120–131°, which was recrystallized three times from ethanol to give red needles, m.p. and mixed m.p. 152°. The higher-boiling fraction yielded a mixture of 2,4-dinitrophenylhydrazones (0.04 g., 50%), melting in the range of 75–90°, which was chromatographed on alumina (1.5 g.). Elution with 1 cc. of carbon tetrachloride followed by recrystallization from ethanol afforded the derivative of the Δ^1-3-ketone (VIa), m.p. and mixed m.p. 152°. Further elution of the chromatogram with 5 cc. of carbon tetrachloride gave the derivative of *3-keto-9-methyl-$\Delta^{1,4}$-hexahydronaphthalene* (XV), m.p. 130°[30] (after crystallization from ethanol). It showed no depression of the melting point on admixture with a sample prepared by the method reported by Woodward and Singh.[33]

In another run, dibromination of the *cis*-ketone (Ia) was conducted in the same solvent at a somewhat higher temperature. Thus, 0.21 g. of Ia in 2 cc. of glacial acetic acid was treated with 0.42 g. of bromine in 2 cc. of the same solvent under ice-cooling, with stirring. After the complete addition of bromine, the yellow solution was slowly warmed to 50°, and this temperature was maintained for 30 min. on a water bath. The water bath was removed, the stirring was continued for 4 hr., and the white precipitate (0.16 g., 39%), m.p. 158–160°, was filtered. The mother liquor, after standing in a refrigerator overnight, was evaporated under reduced pressure to give additional crystals (0.16 g., total 78%), m.p. 158–160° (after washing with petroleum ether). Two recrystallizations from petroleum ether gave colorless needles, m.p. 160–161°.

Anal. Calcd. for $C_{11}H_{16}Br_2O$: C, 40.74; H, 4.98. Found: C, 40.41; H, 5.05.

The solid dibromo ketone differed somewhat from the liquid one in behavior toward bases.

Reaction of cis-2,4-dibromo-9-methyl-3-decalone (XIVa) *with anhydrous sodium acetate.* The dibromo ketone (XIVa), used for acetolysis, was prepared from the *cis*-ketone (Ia, 0.50 g.) with 2 moles of bromine (0.98 g.) in chloroform under the conditions employed for the monobromo ketone (IIa). Acetolysis of the crude dibromo ketone (1.0 g.) was carried out, exactly following the procedure reported for the *trans*-dibromo ketone (XIVb).[3] A neutral product, containing *cis-2-acetoxy-3-keto-9-methyl-Δ^1-octahydronaphthalene* (XVIa), was obtained as a colorless viscous oil (0.50 g., 75%), b.p. 127–143° at 4 mm. Redistillation gave an oil, b.p. 130–135° at 4 mm.; λ_{max}^{MeOH} 239 mμ (ϵ 2300).

Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.06; H, 8.22.

The alkali-soluble fraction afforded a small amount of a yellow viscous oil (0.03 g., 5.5%), containing mainly the above 2,3-diketone (VIIIa). It showed dark blue–violet coloration with ferric chloride. The glyoxime, m.p. 195–199°, was obtained in 72% yield, which was recrystallized from methanol to give prisms, m.p. and mixed m.p. 200–201°.

Reaction of cis-2-acetoxy-3-keto-9-methyl-Δ^1-octahydronaphthalene (XVIa) *with alkali.* The acetoxy-Δ^1-3-ketone (XVIa, 0.30 g.) was treated with 6% methanolic potassium hydroxide (5.1 cc.) as described above for the *cis*-2-acetoxy ketone (VIa). The starting material (0.02 g., 7%) was recovered as a neutral fraction. The alkali-soluble fraction afforded a pale yellow oil (0.11 g.) which was distilled to give 0.10 g. (40%) of the 2,3-diketone (VIIIa), as a colorless oil, b.p. 103–104° at 3 mm. It gave blue-violet coloration with ferric chloride and formed a glyoxime, m.p. and mixed m.p. 200–201° (after crystallization from methanol). The bicarbonate-soluble fraction gave an oil (0.12 g., 41%) which mostly solidified. Recrystallization from ethyl acetate afforded the *cis*-diacid (VIIa) as colorless prisms, m.p. and mixed m.p. 189–190°.

Lithium aluminum hydride reduction of cis-9-methyl-3-decalone (Ia). *Formation of cis-9-methyl-cis-3-decalol* (XVII). To a stirred solution of 0.5 g. of the *cis*-ketone (Ia) in 20

(30) Yanagita and Yamakawa, *J. Org. Chem.*, **20**, 1473 (1955).

(31) This experimentation was carried out by M. Hirakura in our Laboratory.

(32) Linstead, Millidge, and Walpole (ref. 10) reported that dehydration of *cis*-9-methyl-2-decalol afforded an impure 9-methyl-Δ^2-octalin (XIII), b.p. 78–80° at 12 mm., which was oxidized with permanganate in aqueous sodium carbonate to give the *cis*-diacid (VIIa) in about 8% yield.

(33) Woodward and Singh, *J. Am. Chem. Soc.*, **72**, 494 (1950).

cc. of absolute ether was added, dropwise, a solution of lithium aluminum hydride in 30 cc. of the same solvent with shaking. A slightly exothermic reaction took place to give a white precipitate. The mixture was heated to reflux on a water bath for 3 hr. After processing in the usual manner, 0.50 g. (quantitatively) of *cis*-9-methyl-*cis*-3-decalol (XVII) was obtained as white crystals, m.p. 62–66°. Recrystallization from petroleum ether gave colorless prisms, m.p. 67.5°. The infrared absorption spectrum; 1007 m, 1034 s, 1058 s, 1088 m cm $^{-1}$ (Fig. 1). Hussey, Liao, and Baker gave m.p. 67° for 9-methyl-*cis*-3-decalol prepared from the *cis*-ketone (Ia) by catalytic hydrogenation.[18]

Anal. Calcd. for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.15; H, 11.94.

An *acetate*, prepared with acetic anhydride and pyridine, was obtained as a colorless oil, b.p. 130–135° (bath-temperature) at 5 mm. The infrared absorption spectrum is shown in Fig. 1.

The decalol (XVII) formed, in 94% yield, a *3,5-dinitrobenzoate*, m.p. 93–97.5°, which was recrystallized from *n*-hexane to give colorless needles, m.p. 98–99°. The above authors[17] gave m.p. 97.5–98.5°.

Anal. Calcd. for $C_{18}H_{20}N_2O_6$: C, 59.99; H, 5.59; N, 7.77. Found: C, 60.23; H, 5.87; N, 7.88.

A mixture of equimolar amounts of the 3,5-dinitrobenzoate (0.06 g.) and α-naphthylamine (0.03 g.) was dissolved into a few drops of ethanol. Without delay, an *addition compound* (0.08 g., 97%) separated as orange crystals. Recrystallization from petroleum ether gave orange plates, m.p. 101.5–102°.

Anal. Calcd. for $C_{28}H_{29}N_3O_6$: C, 66.78; H, 5.81; N, 8.35. Found: C, 66.42; H, 6.19; N, 8.48.

To a solution of 0.17 g. of the decalol (XVII) in 2 cc. of pyridine and 2 cc. of anhydrous benzene was added 0.30 g. of anthraquinone-β-carboxylic chloride, and was allowed to stand 5 days. The separated solid was filtered and washed with ether, and the filtrate, combined with the ether washing, was worked up by the procedure reported previously.[34] There was obtained a yellow viscous oil (0.19 g.), which upon treatment with petroleum ether gave 0.11 g. (24%) of yellow crystals, m.p. 111–115°. Two recrystallizations from petroleum ether afforded light yellow prisms, m.p. 123–126°.

Anal. Calcd. for $C_{26}H_{26}O_4$: C, 77.59; H, 6.51. Found: C, 76.99; H, 6.84.

Attempted hydrogenation of the *cis*-ketone (Ia, 0.05 g.) over platinum dioxide (0.01 g.) in acidic medium under normal pressure was made, but the starting ketone was quantitatively recovered.

trans-9-Methyl-cis-3-decalol (XVIII). This was prepared by reduction of *cis*-9-methyl-3-decalone (Ia, 0.30 g.) with sodium (1.0 g.) and ethanol (30 cc.),[35] exactly following the procedure described earlier for the *trans*-ketone (Ib).[4] There was obtained a yellow oil (0.28 g.), which was chromatographed on alumina (6 g.). Elution with petroleum ether afforded 0.08 g. (27%) of the starting ketone, m.p. and mixed m.p. 46°. Further elutions with petroleum ether-benzene (1:1) (10 cc.) and benzene (10 cc.) gave a pale yellow oil (0.115 g., 37%), giving no precipitate with Brady's reagent. This oil formed quantitatively an oily 3,5-dinitrobenzoate (0.23 g.), which could not be induced to crystallize and was chromatographed on alumina (6 g.). Elutions with petroleum ether (30 cc.) and with benzene (10 cc.) yields, respectively, 105 mg. and 65 mg. (total 74%) of a colorless oil, which, by the procedure described above for the same derivative of XVII, formed quantitatively an α-naphthylamine addition compound, m.p. 95–99°. An oily residue (60 mg.) from elution with benzene-ether (1:1) (50 cc.) gave no crystalline compound with α-naphthylamine. The addition compound was recrystallized from petroleum ether to give orange needles, m.p. 104–105°. On admixture with the addition compound of the *cis,cis*-decalol (XVII), the melting point was slightly depressed to 98–100°.

Anal. Calcd. for $C_{28}H_{29}N_3O_6$: C, 66.78; H, 5.81; N, 8.55. Found: C, 66.60; H, 6.06; N, 8.07.

Reduction of the *cis*-ketone (Ia) with sodium and amyl alcohol gave in a better yield the decalol (XVIII) of higher purity. To a refluxed solution of 0.30 g. of the *cis*-ketone in 30 cc. of amyl alcohol (b.p. 130–135°) in an oil bath was added, in small portions, 1.2 g. of sodium metal during 20 min. After violent reaction subsided, the reflux was continued further for 2 hr. On cooling, the mixture was diluted with ether and washed repeatedly with water. The organic layer was evaporated under reduced pressure, the residual oil was dissolved in ether, and dried over anhydrous sodium sulfate. Evaporation of the ether and subsequent distillation of the residual oil gave 0.24 g. (79%) of the *trans,cis*-decalol (XVIII), as a colorless oil, b.p. 104–107° at 4.5 mm. It could not be induced to crystallization even after redistillation (b.p. 104–106° at 4.5 mm.). The infrared absorption spectrum; 1007 m, 1022 s, 1034 s, 1054 s, 1086 w cm.$^{-1}$ (Fig. 1). This oil formed quantitatively an oily 3,5-dinitrobenzoate, which afforded a quantitative yield of α-naphthylamine addition compound, m.p. and mixed m.p. 104–105° (after recrystallization from petroleum benzine).

An *acetate*, prepared with acetic anhydride and pyridine, was obtained as a colorless oil, b.p. 115–116° at 6 mm. The infrared absorption spectrum is shown in Fig. 1.

By the procedure described above for the *cis,cis*-decalol (XVII), this oil (0.08 g.) was converted to an anthraquinone-β-carboxylate (0.02 g., 10%), light yellow prisms, melting in the range 112–130°. Two recrystallizations from petroleum benzine raised the m.p. to 153–155.5°.

Anal. Calcd. for $C_{26}H_{26}O_4$: C, 77.59; H, 6.51. Found: C, 78.37; H, 7.08.

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(34) Reichstein, *Helv. Chim. Acta*, **9**, 805 (1926).

(35) Correction; reference 4, page 1770, line 4, read "30 cc. of ethanol" instead of "300 cc. of ethanol."

[CONTRIBUTION FROM THE FULMER CHEMICAL LABORATORY, THE STATE COLLEGE OF WASHINGTON]

Preparation of Some Aminotrifluoromethyldiphenyl Sulfones as Possible Antibacterial Agents[1]

GARDNER W. STACY, C. RICHARD BRESSON,[2] ROBERT E. HARMON,[3] AND RICHARD C. THAMM[4]

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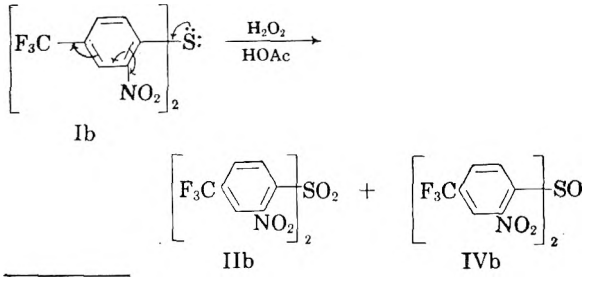
The preparation of six aminotrifluoromethyldiphenyl sulfones by way of the corresponding intermediate nitro sulfones and sulfides is described. An observation concerning the relative ease of oxidation of nitrotrifluoromethyldiphenyl sulfides to their corresponding sulfones is discussed. Of the six aminotrifluoromethyldiphenyl sulfones submitted for chemotherapy screening only the 4,4′-diamino-2-trifluoromethyldiphenyl sulfone (IIIc) showed appreciable antibacterial activity (*vs. Streptococcus pyogenes*). These results are in agreement with the principle previously established by others that amino groups in diphenyl sulfones must be situated in both *para*- positions for appreciable activity.

In previous studies by others[5] on the correlation of the structure of diaminodiphenyl sulfones with antibacterial activity, appreciable activity had been found primarily in those cases where the phenyl groups carried amino substituents in both *para*- positions. Further nuclear substitution of other groups seemed to minimize activity. We wished to study this correlation further in an additional series of substituted amino- and diaminodiphenyl sulfones, for any marked contradication to the established pattern obviously would be of interest. The trifluoromethyl group[6] was selected as the substituent to be incorporated into the present series because of interest in fluorine-substituted compounds in medicinal chemistry.[7]

The preparation of the various aminotrifluoromethyldiphenyl sulfones (Table III), which were of interest in the present study, was accomplished by the well known approach involving the corresponding nitro sulfides (Table I) and nitro sulfones (Table II) as intermediates. The unsymmetrical sulfides (Ic,d,e,f) were formed readily by the reaction of the appropriate chloronitrobenzotrifluoride with sodium *p*-nitrothiophenolate or sodium thiophenolate. The usual procedure for obtaining symmetrical sulfides such as Ia,b involves the reaction of an activated aryl halide with sodium sulfide.[6,8] A less well known procedure, which has shown promise of being superior to the sodium sulfide method, utilizes potassium ethyl xanthate as the source of the sulfide sulfur atom.[9] This method has been employed in the present work for the synthesis of symmetrical sulfides. Excellent results were obtained particularly in the case of the sulfide Ib where the yield of recrystallized product was 79%. Of comparative interest was the fact that the sulfide Ia was obtained in a crude yield of 69% (recrystallized product, 60%), wherein Caldwell and Sayin had obtained a 49% crude yield by the sodium sulfide method.[6]

In four cases, the hydrogen peroxide oxidation of nitrotrifluoromethyldiphenyl sulfides to the corresponding sulfones, either in glacial acetic acid or glacial acetic acid–acetic anhydride as solvent, gave excellent yields (85% to quantitative). However, in the case of the sulfide Ib, the corresponding sulfone IIb was obtained in a yield of only 23%. From the crude product, there also was isolated a small amount of the corresponding sulfoxide IVb (13%).



(1) Presented in part before a Northwest Regional Meeting of the American Chemical Society, Seattle, Wash., June 12, 1956.

(2) Abstracted in part from a thesis submitted by C. Richard Bresson in partial fulfillment of the requirements for the degree of Master of Science, the State College of Washington, February 1955.

(3) A portion of this work was carried out by Robert E. Harmon as an undergraduate research project, Senior in Chemistry, 1953–54.

(4) Abstracted in part from a thesis submitted by Richard C. Thamm, in partial fulfillment of the requirements for the degree of Bachelor of Science with Distinction, February, 1953.

(5) (a) Roblin, Williams, and Anderson, *J. Am. Chem. Soc.*, **63**, 1930 (1941); (b) Baker, Kadish, and Querry, *J. Org. Chem.*, **15**, 400 (1950).

(6) After this project had been initiated, Caldwell and Sayin, *J. Am. Chem. Soc.*, **73**, 5125 (1951), reported trifluoromethyl derivatives of *p*-aminobenzoic acid, sulfanilamide, and, of pertinent interest to the present subject, *p,p′*-diaminodiphenyl sulfone.

(7) A few representative references in respect to this point are: (a) Snyder, Freier, Kovacic, and Van Heyningen, *J. Am. Chem. Soc.*, **69**, 371 (1947); (b) Lindenstruth and Vander Werf, *J. Am. Chem. Soc.*, **73**, 4209 (1951); (c) Hauptschein, Nodiff, and Saggiomo, *J. Am. Chem. Soc.*, **76**, 1051 (1954).

(8) Connor in Gilman, ed., *Organic Chemistry*, 2nd ed., John Wiley and Sons, New York, N. Y., 1943, Vol. I, p. 855.

(9) Price and Stacy, *Org. Syntheses*, Coll. Vol. III, 667 (1955).

TABLE I
NITROTRIFLUOROMETHYLDIPHENYL SULFIDES

Sulfide	Yield, %[a]	Recryst. Solvent[b]	M.p., °C.[c]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
bis-(4-Nitro-2-trifluoromethylphenyl) (Ia)	60	A	136–137[d]	$C_{14}H_6F_6N_2O_4S$						
bis-(2-Nitro-4-trifluoromethylphenyl) (Ib)	79[e]	A	144–145	$C_{14}H_6F_6N_2O_4S$	40.77	40.57	1.47	1.43	6.80	6.86
4,4′-Dinitro-2-trifluoromethyldiphenyl (Ic)	55	A	162.5–163.5	$C_{13}H_7F_3N_2O_4S$[f]	45.35	45.37	2.05	1.97	9.31	9.43
2,4′-Dinitro-4-trifluoromethyldiphenyl (Id)	38[e]	E	129–130	$C_{13}H_7F_3N_2O_4S$	45.35	45.39	2.05	2.15	9.31	9.49
4-Nitro-2-trifluoromethyldiphenyl (Ie)	81		Sirup	$C_{13}H_8F_3NO_2S$						
2-Nitro-4-trifluoromethyldiphenyl (If)	68[e]	E	72.5–73.5[g]	$C_{13}H_8F_3NO_2S$	52.15	52.20	2.76	2.81	10.73	10.56

[a] Yields reported in all Tables are those of the recrystallized products. [b] Analytical samples were recrystallized several times in each instance (all Tables). Solvents employed: A, glacial acetic acid; E, 95% ethanol. [c] M.p. of analytical sample (all Tables). All of these sulfides had the appearance of bright yellow needles or platelets. [d] Caldwell and Sayin (ref. 6) reported m.p. 136–137°. [e] 4-Chloro-3-nitrobenzotrifluoride (ref. 13) was used in the preparation of these sulfides. [f] N calcd. 8.14; found 8.15. [g] Bunnett and Davis, *J. Am. Chem. Soc.*, 76, 3011 (1954), reported m.p. 71–72°.

TABLE II
NITROTRIFLUOROMETHYLDIPHENYL SULFONES

Sulfone	Yield,[a] %	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
bis-(4-Nitro-2-trifluoromethylphenyl) (IIa)	86A, 94B[b]	172–173[c]	$C_{14}H_6F_6N_2O_6S$						
bis-(2-Nitro-4-trifluoromethylphenyl) (IIb)	23B, 66C	168–168.5	$C_{14}H_6F_6N_2O_6S$	37.85	37.69	1.36	1.34	7.22	7.07
4,4′-Dinitro-2-trifluoromethyldiphenyl (IIc)	98A	193–194	$C_{13}H_7F_3N_2O_6S$	41.49	41.27	1.88	1.81	8.52	8.37
2,4′-Dinitro-4-trifluoromethyldiphenyl (IId)	41A, 74C	174–174.5	$C_{13}H_7F_3N_2O_6S$	41.49	41.57	1.88	1.82	8.52	8.69
4-Nitro-2-trifluoromethyldiphenyl (IIe)	84B[b]	159–160	$C_{13}H_8F_3NO_4S$	47.12	47.03	2.45	2.53	9.69	9.58
2-Nitro-4-fluoromethyldiphenyl (IIf)	85B[b]	148–149	$C_{13}H_8F_3NO_4S$	47.12	46.99	2.45	2.48	9.69	9.80

[a] Capital letters denote procedure used for the preparation of the sulfone. [b] Recrystallized from 85% acetic acid. The other sulfones were recrystallized from glacial acetic acid. All of the nitro sulfones had the appearance of fine, colorless needles. [c] Caldwell and Sayin (ref. 6) reported m.p. 172–173°.

TABLE III
AMINOTRIFLUOROMETHYLDIPHENYL SULFONES

Sulfone	Yield, %	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Funod	Sulfur, % Calcd.	Sulfur, % Found
bis-(4-Amino-2-trifluoromethylphenyl) (IIIa)	88[a]	210–211[b]	$C_{14}H_{10}F_6N_2O_2S$						
bis-(2-Amino-4-trifluoromethylphenyl) (IIIb)	45[c]	139–139.5	$C_{14}H_{10}F_6N_2O_2S$	43.75	43.75	2.62	2.62	8.34	8.15
4,4′-Diamino-2-trifluoromethyldiphenyl (IIIc)	95[d]	193.5–194.5[e]	$C_{13}H_{11}F_3N_2O_2S$	49.36	49.13	3.51	3.70	10.14	10.28
2,4′-Diamino-4-trifluoromethyldiphenyl (IIId)	65[f]	197–198	$C_{13}H_{11}F_3N_2O_2S$	49.36	49.46	3.51	3.64	10.14	10.02
4-Amino-2-trifluoromethyldiphenyl (IIIe)	71[g]	186.5–187.5	$C_{13}H_{10}F_3NO_2S$	51.82	51.59	3.35	3.35	10.64	10.40
2-Amino-4-trifluoromethyldiphenyl (IIIf)	73[h]	141–141.5	$C_{13}H_{10}F_3NO_2S$	51.82	51.77	3.35	3.39	10.64	10.42

[a] Purified by precipitating from 15% hydrochloric acid with 30% potassium hydroxide solution. All amino sulfones had the appearance of colorless needles or platelets. [b] Reported melting point 211–212° (ref. 6); melts with decomposition. [c] Recrystallized from 85% acetic acid. [d] Recrystallized from 80% ethanol in which was dissolved 0.01 g. of sodium hydrosulfite as an antioxidant to prevent discoloration through oxidation. [e] In a mixed melting point determination with the starting material (m.p. 193–194°, IIc, Table II), a considerable depression was observed (m.p. 160–165°). [f] Recrystallized from 60% ethanol. [g] Purified by precipitating from hot 30% hydrochloric acid solution with cold water. A residual insoluble oil was taken up in 60% ethanol, precipitated with water, filtered, dried, and treated again with hot 30% hydrochloric acid. This procedure brought about solution and purification of most of the crude product. [h] Recrystallized from 65% ethanol.

It was of interest to note that the sulfoxide IVb, m.p. 167–167.5°, had almost identically the same melting point as the sulfone IIb, m.p. 168–168.5°. Admixture of the two, however, resulted in a marked depression in melting point (132–136°).

Since the isomeric sulfide Ia underwent oxidation with hydrogen peroxide in glacial acetic acid under precisely the same conditions as the experiment with Ib to yield 94% of the pure, recrystallized sulfone IIa, the result just described relative to Ib suggested a considerably decreased tendency toward oxidation. A parallel situation in respect to oxidation also was observed for the isomeric sulfides Ic,d. Here again, the isomer with a nitro group in an *ortho-* position underwent oxidation with much greater difficulty. Difficulties in oxidizing sulfides to sulfones have been reported previously.[10] For the most part, such difficulties in oxidation were attributed to steric factors. Although undoubtedly steric hindrance in many instances would account for resistance to oxidation, in the present case it would not seem to be an important factor in explaining the results observed. Indeed, since the trifluoromethyl group is larger in size than the nitro group,[11] the direct opposite of what was observed might have been anticipated if steric hindrance was of major importance. On the other hand, the observed variations in ease of oxidation might be explained readily on the basis of electrical effects. The effect of the electron-withdrawing nitro and trifluoromethyl groups would tend to diminish the electron density on the sulfur atom for the sulfides in question (*cf.* formula Ib). To the extent that the *ortho*-nitro and *para*-trifluoromethyl combination was more effective in decreasing the sulfur electron density than in the case of the isomer, one would anticipate greater difficulty in oxidation. It is not unreasonable to conclude that this situation, indeed, obtains, for it is well known that the nitro group is a stronger electron-withdrawing group than the trifluoromethyl group and that it would be more effective in this capacity in the *ortho-* position than in the *para.*

Use of a much more vigorous oxidizing agent, chromic anhydride, expedited the preparation of the sulfones IIb,d in good yield and free of contaminating sulfoxide.

Initially, reduction of nitro sulfones to amino sulfones was attempted by means of a catalytic procedure using Raney nickel. In the case of the reduction of IIf to IIIf, the procedure was applied with good results (73% yield). But when we attempted to extend the procedure to the isomer IIe and the symmetrical sulfone IIb, we were unable to obtain the desired amino sulfones Reduction by stannous chloride proved successful, however, and was employed, therefore, for preparation of all the other amino sulfones. Generally, the yields obtained were excellent (71–95%); however, two sulfones IIb,d gave less satisfactory yields, 45 and 65%, respectively. This result appeared to be correlated with one or both nitro groups being situated in the *ortho-* positions. Another case of the product and the starting material having virtually the same melting point was encountered in the amino sulfone series. The nitro sulfone IIc, m.p. 193–194°, was found to yield an amino sulfone IIIc with a melting point of 193.5–194.5°. Admixture of these two substances lead to a considerable depression in the melting point (160–165°).

In one run for the preparation of nitro sulfone IIa, an unexpected result was observed. A small amount of higher melting substance (206–207° *vs.* 172–173° for IIa) was isolated. Analysis confirmed its percentage composition as being that of IIa; therefore, one would conclude that it was an isomer or dimorphic form. The latter possibility appeared to be ruled out, for on reduction, the substance yielded an amino sulfone IIIa′ of higher melting point than IIIa (236–237° *vs.* 210–211°). The nature of these compounds was not investigated further.

Chemotherapy screening. None of the aminotrifluoromethyldiphenyl sulfones (Table III), with one exception, was found to be effective for mice infected with any of the following organisms: influenza virus, MM virus, *Streptococcus pyogenes*, Typhoid, *Proteus vulgaris*, or *Psuedomonas aeruginosa.* Only 4,4′-diamino-2-trifluoromethyldiphenyl sulfone (IIIc) showed appreciable antibacterial activity (*vs.* 2350 Ld_{50} in *Streptococcus pyogenes* infected mice at 10 mg. subq. × 2). Also it was interesting to note that compounds containing as much as one *ortho-* amino substituent were more toxic than those with no *ortho-* amino substituents. Thus, these results further substantiate the correlations of structure and activity observed by others.[5]

EXPERIMENTAL[12]

2-Chloro-5-nitrobenzotrifluoride. Substantially in accord with the procedure of Caldwell and Sayin,[6] 179.5 g. (1.00 mole) of *o*-chlorobenzotrifluoride[13] was added dropwise with stirring to a nitrating mixture consisting of 200.0 g. of concentrated sulfuric acid and 81.0 g. of fuming nitric acid. The temperature of the reaction mixture was maintained at 30–35° by controlling the addition of the reactant and cooling the mixture in an ice bath. After addition was complete, stirring of the mixture was continued for 30 min. at room temperature and then at 60° (water-bath). When the mixture had cooled to room temperature, the lower phase of spent acid was removed, and the crude organic

(10) (a) Baker, Querry, and Kadish, *J. Org. Chem.*, **15**, 402 (1950); (b) Horner and Medem, *Chem. Ber.*, **85**, 520 (1952); (c) Blanksma, *Rec. trav. chim.*, **20**, 425 (1901).

(11) From Fischer-Taylor-Hirschfelder models, the interference radii of the trifluoromethyl and nitro groups were determined as being 2.50 Å. and 2.35 Å., respectively.

(12) All melting points are corrected, and boiling points are uncorrected. The microanalytical work was performed by Galbraith Laboratories, Knoxville, Tenn.

(13) Obtained from Halogen Chemicals, Inc., Columbia 3, S. C.

material was washed successively with two 150-ml. portions of water, three 100-ml. portions of 2% sodium carbonate solution, and finally again with two 100-ml. portions of water. After drying over anhydrous magnesium sulfate, the product was distilled under reduced pressure; yield, 183.0 g. (81%), b.p. 64–66° (2–3 mm.), n_D^{25} 1.5058. Since the boiling point seemed somewhat lower than might have been anticipated from those previously reported,[14] a sample was submitted for analysis.

Anal. Calcd. for $C_7H_3ClF_3NO_2$: C, 37.27; H, 1.34; N, 6.21. Found: C, 37.12; H, 1.21; N, 6.16.

Further, a sample was converted into the acetyl derivative of the corresponding amine, the melting point of which (m.p. 117–117.5°) was in agreement with that reported previously.[6]

Unsymmetrical sulfides. The procedure[15] employed for the preparation of the sulfide Ic (Table I) exemplifies that used for the synthesis of unsymmetrical sulfides. To a solution of 19.3 g. (0.12 mole) of *p*-nitrothiophenol[16] in 120 ml. of absolute ethanol was added 2.85 g. (0.12 gram atom) of sodium in small pieces. To this then was added dropwise with stirring a solution of 28.0 g. (0.12 mole) of 2-chloro-5-nitrobenzotrifluoride in 130 ml. of absolute ethanol. The reaction mixture was heated under reflux for 90 min. and was cooled overnight and filtered. The product was washed with 200 ml. of hot water and dried; yield 27.7 g. (65%), m.p. 149–151°.

Symmetrical sulfides. These were prepared by the xanthate method,[9] and the details for the preparation for the sulfide Ia are illustrative. To a solution of 48.3 g. (0.30 mole) of potassium ethyl xanthate in 200 ml. of 95% ethanol was added 67.7 g. (0.30 mole) of 2-chloro-5-nitrobenzotrifluoride, and the mixture was heated under reflux for 24 hr. The reaction mixture then was diluted with 100 ml. of water and cooled. The resulting precipitate was removed by filtration and washed with hot water and cold ethanol; yield, 42.4 g. (68%), m.p. 128–131°.

Nitro sulfoxides and sulfones. Procedure A. Hydrogen peroxide oxidation in glacial acetic acid–acetic anhydride. The procedure[17] as specifically applied to conversion of the sulfide Ia to the corresponding sulfone IIa is presented. A mixture of 3.90 g. (9 mmoles) of the sulfide Ia and 45 ml. of an 8:1 glacial acetic acid–acetic anhydride solution was heated to 85–90°. After solution had occurred, 5 ml. (*ca.* 0.045 mole) of 30% hydrogen peroxide was added dropwise, and then the solution was heated under reflux for 1 hr. The fine, colorless needles were removed by filtration, washed with cold 85% acetic acid, and dried (Table II).

In one run involving the preparation of IIa from 32.4 g. (0.078 mole) of Ia by this method, an unusual result was observed. In crystallizing from the reaction mixture, the product separated into two fractions: A, 6.11 g., m.p. 191.5–192.5° and B, 21.6 g., m.p. 166–169°. Fraction B was IIa, but recrystallization of A gave a substance of considerably higher melting point (m.p. 206–207°). Although the nature of this compound has not been fully determined, analysis suggested it to be an *isomer of IIa* (*IIa'*).

Anal. Calcd. for $C_{14}H_6F_6N_2O_6S$: C, 37.85; H, 1.36; S, 7.22. Found: C, 38.02; H, 1.28; S, 7.10.

Procedure B. Hydrogen peroxide oxidation in glacial acetic acid. Although this procedure was employed in the oxidation of several sulfides to sulfones, its application to bis-(2-nitro-4-trifluoromethylphenyl) sulfide (Ib → IIb) is presented because of its particular interest. To 10.0 g. (0.023 mole) of Ib dissolved in 100 ml. of glacial acetic acid, which had been heated to 90°, was added dropwise 14 ml. of 30% hydrogen peroxide with stirring. The temperature was maintained at 90° for 2 hr., and then the mixture was heated under reflux for 1 hr. Finally an additional 8 ml. of hydrogen peroxide was added, and refluxing was continued for 1 hr. The mixture was allowed to cool overnight, and the yellow crystalline precipitate was removed by filtration; yield, 4.68 g., m.p. 142–145°. The filtrate was concentrated and yielded an additional 1.60 g., m.p. 128–132°. These two substances were subjected to fractional crystallization from glacial acetic acid and water (concentration adjusted by addition of small portions). There were obtained 3.45 g. (23%) of colorless needles (m.p. 168–168.5°), which was the sulfone IIb (compare with the material obtained by *Procedure C* below), and 1.33 g. (13%) of yellow platelets (m.p. 167–167.5°). This latter substance was *bis-(2-nitro-4-trifluoromethylphenyl) sulfoxide (IVb).*

Anal. Calcd. for $C_{14}H_6F_6N_2O_5S$: C, 39.24; H, 1.43; N, 6.54. Found: C, 39.29; H, 1.42; N, 6.49.

Admixture of the pure sulfone and sulfoxide resulted in a sharply depressed melting point (132–136°).

2,4'-Dinitro-4-trifluoromethyl sulfoxide. When *Procedure A* was applied to 13.0 g. (0.038 mole) of the sulfide Id, only partial oxidation to the sulfone IId took place. There was obtained initially 11.0 g. (78%) of yellow needles, m.p. 164–167°. Fractional recrystallization of this product gave 5.80 g. (41%) of sulfone, m.p. 174–174.5°, and 1.60 g. (11%) of the corresponding sulfoxide, m.p. 134.5–135°.

Anal. Calcd. for $C_{13}H_7F_3N_2O_5S$: C, 43.34; H, 1.96; S, 8.90. Found: C, 43.54; H, 1.96; S, 9.10.

Procedure C. Chromic anhydride oxidation. This method[18] is briefly outlined as applied to the preparation of the sulfone IIb. To 2.72 g. (6.6 mmoles) of Ib dissolved in 30 ml. of glacial acetic acid was added 2.00 g. (20 mmoles) of chromic anhydride, as the mixture was being heated under reflux. Heating under reflux was continued for 12 hr., and the reaction mixture then was cooled and poured into water; the greenish white precipitate was removed by filtration and washed with water. When this product was admixed with the sulfone obtained in *Procedure B* above, no depression of melting point was observed.

Amino sulfones. One nitro sulfone was reduced catalytically by the procedure of Gilman and Broadbent.[15] However, the procedure,[19] which was employed in the reduction of all but one of the nitro sulfones, is illustrated as follows by the preparation of bis-(2-amino-4-trifluoromethylphenyl) sulfone (IIIb) (Table III). Anhydrous hydrogen chloride (generated according to Maxson[20]) was introduced into a mixture of 50.0 g. (0.22 mole) of stannous chloride dihydrate, 50 ml. of glacial acetic acid, and 5 ml. of water until the solution became saturated; during this period the mixture was stirred and heated to 80°. Then 9.30 g. (0.022 mole) of the nitro sulfone IIb was added, and when the vigorous reaction had subsided, the solution was heated to 80° for 2 hr. Then the solution was poured into 200 ml. of water and cooled, and the colorless product was removed by filtration and washed with 30% potassium hydroxide solution followed by water.

It was observed that reduction of the nitro sulfones at 80° or above always lead to a considerable amount of color in the product which was difficult to remove. Finally, it was observed (for IIIa and IIId) that discoloration was avoided and that the yields were improved if the reaction temperature was maintained below 55° during the first half hour.

Aminotrifluoromethyldiphenyl sulfone isomer (IIIa'). The

(14) Caldwell and Sayin (ref. 6) reported b.p. 108° (10 mm.), and a French patent reported 102–103° (5 mm.), *Chem. Abstr.*, 27, 4414 (1933).

(15) Gilman and Broadbent, *J. Am. Chem. Soc.*, 69, 2053 (1947).

(16) Price and Stacy, *J. Am. Chem. Soc.*, 68, 498 (1946).

(17) Burton and Hoggarth, *J. Chem. Soc.*, 468 (1945).

(18) Shriner, Struck, and Jorison, *J. Am. Chem. Soc.*, 52, 2060 (1930).

(19) (a) Price, Leonard, and Stacy, *J. Am. Chem. Soc.*, 69, 855 (1947); (b) Amstutz, *J. Am. Chem. Soc.*, 72, 3420 (1950).

(20) Maxson in Booth, Ed., *Inorganic Syntheses*, McGraw-Hill, New York, N. Y., 1939, Vol. I, p. 147.

nitrotrifluoromethyldiphenyl sulfone isomer (IIa'), which had been isolated in the process of the preparation of sulfone IIa, was subjected to reduction by the stannous chloride procedure. From 500 mg. (1.1 mmoles) of IIa' there was obtained 290 mg. (67%) of yellow, granular crystals, m.p. 236–237°.

Anal. Calcd. for $C_{14}H_{10}F_6N_2O_2S$: C, 43.75; H, 2.62; S 8.34. Found: C, 43.78; H, 2.62; S, 8.59.

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PULLMAN, WASH.

[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, RADIUM INSTITUTE, UNIVERSITY OF PARIS]

1,2,2-Triarylethylenes Substituted with Higher Alkyl Groups

NG. PH. BUU-HOÏ AND N. D. XUONG

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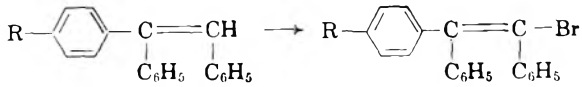
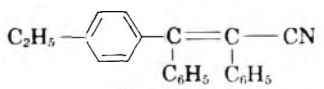
A number of 1-bromo- and 1-cyano-1,2,2-triarylethylenes, bearing higher alkyl groups, and possessing only a weak estrogenic activity, have been synthesized for biological investigation as potential chemical inhibitors of the anterior pituitary secretions.

1,2,-Triarylethylenes, especially those bearing a halogen or a cyano substituent in the ethylene bridge, form a biologically interesting group comprising several substances of remarkably high estrogenic potency (as for instance, 1-bromo- and 1-cyano-1,2,2-triphenylethylene,[1] 1-bromo-1-phenyl-2,2-di(4-ethoxyphenyl)ethylene, 1-chloro-1,2,2-trianisylethylene,[2] etc.) These estrogenic 1,2,2-triarylethylenes are also chemical inhibitors of the secretions of the anterior pituitary,[3] especially of the somatotrophic hormone, and some have found practical use in the chemotherapy of cancer[4]; in this series, the estrogenic activity is known to decrease sharply with the introduction of alkyl substituents in *para-* positions.[1] Now, it has recently been found that some 1,2,-triarylethylenes bearing higher alkyl groups, such as 1-bromo-1,2-diphenyl-2-(4-*n*-butylphenyl)ethylene (III), are good inhibitors of growth in mice, while displaying only a negligible estrogenic activity[5]; compound III inhibits also the effect of gonadotrophin on the ovaries in female mice, but has little action on the development of the testicles in male animals. These observations led us to synthesize, for biological evaluation in this domain, a number of homologs and analogs of compound (III) bearing higher alkyl groups or other bulky substituents in the benzene rings.

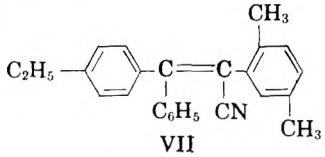


I; R = *n*-C_5H_{11}
II; R = *n*-C_6H_{13}
III; R = *n*-C_4H_9
IV; R = *n*-C_5H_{11}
V; R = *n*-C_6H_{13}

The reaction of benzylmagnesium chloride on 4-*n*-amyl- and 4-*n*-hexylbenzophenone yielded tertiary alcohols which were directly dehydrated with formic acid to 1,2-diphenyl-2-(4-*n*-amylphenyl)- (I) and 1,2-diphenyl-2-(4-*n*-hexylphenyl)ethylene (II), respectively; these liquid hydrocarbons readily underwent bromination to give 1-bromo-1,2-diphenyl-2-(4-*n*-amylphenyl)- (IV) and 1-bromo-1,2-diphenyl-2-(4-*n*-hexylphenyl)ethylene (V), both of which were well crystallized compounds. In these bromination reactions, it was observed that only one of the two possible stereoisomeric ethylenes was formed; on the other hand, the sodium amide–catalyzed condensation of 4-ethylbenzophenone with benzyl cyanide[6] yielded 1,2-diphenyl-2-(4-ethylphenyl)acrylonitrile (VI) in both stereoisomeric forms.



VI



VII

(1) Lacassagne, Buu-Hoï, Corre, Lecocq, and Royer, *Experientia*, **2**, 70 (1946); Robson, Schönberg, and Tadros, *Nature*, **150**, 22 (1942).

(2) Thompson and Werner, *Proc. Soc. Exp. Biol. Med.*, **77**, 484 (1951).

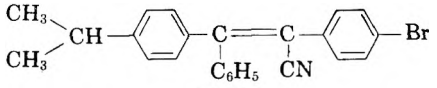
(3) Zondek, *Lancet*, **1**, 10 (1936); **2**, 842 (1936); Noble, J., *Physiol.*, **94**, 177 (1938); *J. Endocrinol.*, **1**, 216 (1939).

(4) Watkinson, Delory, King, and Haddow, *Brit. Med. J.*, **2**, 492 (1944); Berger and Buu-Hoï, *Lancet*, **2**, 172 (1947).

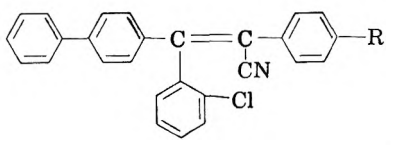
(5) Buu-Hoï, Xuong, and Beauvillain, *Experientia*, in press.

(6) Bodroux, *Bull. soc. chim. France*, **9**, 758 (1911); Buu-Hoï and Lecocq, *J. Chem. Soc.*, 641 (1947); Buu-Hoï, Lecocq, and Hoán, *Bull. soc. chim. France*, **14**, 816 (1947); Buu-Hoï, Hoán, Lecocq, and Declercq, *Rec. trav. chim.*, **67**, 796 (1948).

The isolation of two stereoisomeric compounds is not possible in all the Bodroux syntheses of 1,2,2-triarylacrylonitriles. For instance, the condensation of 4-ethylbenzophenone with 2,5-dimethylbenzyl cyanide yielded only one 1-(2,5-dimethylphenyl)-2-phenyl-2-(4-ethylphenyl)acrylonitrile (VII); similarly, in the reaction of 4-isopropylbenzophenone with *p*-bromobenzyl cyanide, only one 1-(4-bromophenyl)-2-phenyl-2-(4-isopropylphenyl)acrylonitrile (VIII) could be isolated.



VIII



IX; R = Br
X; R = Cl

Other 1,2,2-triarylacrylonitriles with bulky substituents were prepared by the Bodroux condensation of 2-chloro-4′-phenylbenzophenone with *p*-bromo- and *p*-chlorobenzyl cyanide, which afforded 1-(4-bromophenyl)-2-(2-chlorophenyl)-2-(4-xenyl)acrylonitrile (IX) and 1-(4-chlorophenyl)-2-(2-chlorophenyl)-2-(4-xenyl)acrylonitrile (X), respectively.

The estrogenic activity of all these new compounds, determined by means of the Allen-Doisy test in rats, was found to be of a very low order; the other biological properties are being investigated.

EXPERIMENTAL

4-n-Amylbenzophenone. To a water-cooled solution of 23 g. of *n*-amylbenzene (prepared from *n*-valerophenone by Kishner-Wolff reduction, using Huang-Minlon's technique[7]) and 32 g. of benzyl chloride in 200 ml. of dry carbon disulfide, 36 g. of finely powdered aluminum chloride was added in small portions with stirring, and the mixture left overnight at room temperature. After decomposition with ice, the organic layer was washed with dilute hydrochloric acid, then with water, dried over sodium sulfate, and the solvent was distilled. Vacuum-fractionation of the residue gave 23 g. of a pale yellow oil, b.p. 232°/18 mm., n_D^{23} 1.5708.

Anal. Calcd. for $C_{18}H_{20}O$: C, 85.7; H, 8.0. Found: C, 85.8; H, 8.0.

The corresponding *2,4-dinitrophenylhydrazone* crystallized from ethanol in shiny yellow leaflets, m.p. 160°.

Anal. Calcd. for $C_{24}H_{24}N_4O_4$: N, 12.9. Found: N, 12.6.

1,2-Diphenyl-2-(4-n-amylphenyl)ethylene (I). To an ice-cooled Grignard solution prepared from 3 g. of magnesium and 12 g. of benzyl chloride in anhydrous ether, 15 g. of the foregoing ketone was added in small portions with stirring, and the mixture refluxed for 10 min. on the water bath. After treatment with an ice-cooled dilute aqueous solution of sulfuric acid, the organic layer was washed with water, the ether was distilled off, and the oily residue was added to 15 g. of pure formic acid. The mixture was then refluxed for 5 min., and water was added after cooling. The dehydration product was taken up in benzene, the benzene solution washed with water and dried over sodium sulfate, the solvent was removed, and the residue was vacuum-fractionated. Yield: 17 g. of a pale yellow, viscous oil, b.p. 271–272°/25 mm., n_D^{22} 1.6233.

Anal. Calcd. for $C_{25}H_{26}$: C, 92.0; H, 8.0. Found: C, 92.1; H, 8.1.

1-Bromo-1,2-diphenyl-2-(4-n-amylphenyl)ethylene (IV). Bromination in acetic acid medium and in the cold was unsatisfactory, and the following procedure was adopted. To a solution of 6.5 g. of the foregoing ethylene in 30 ml. of dry chloroform, 3.2 g. of bromine (in 20 ml. of chloroform) was added in small portions with stirring, and the mixture heated for 2 hr. at 50–60° on the water bath. The residue from evaporation of the solvent was washed with water and recrystallized twice from acetic acid or ethanol, giving fine colorless prisms, m.p. 100°. Yield: 6 g. No isomer was found in the mother liquors.

Anal. Calcd. for $C_{25}H_{25}Br$: C, 74.1; H, 6.2. Found: C, 74.2; H, 6.0.

4-n-Hexylbenzophenone. Prepared, as for the lower homolog, from 65 g. of *n*-hexylbenzene, 75 g. of benzoyl chloride, and 85 g. of aluminum chloride in carbon disulfide medium, this *ketone* was a pale yellow, viscous oil, b.p. 239–240°/18 mm., n_D^{24} 1.5621. Yield: 83 g.

Anal. Calcd. for $C_{19}H_{22}O$: C, 85.7; H, 8.3. Found: C, 85.6; H, 8.2.

The *2,4-dinitrophenylhydrazone* crystallized from ethanol in shiny yellow leaflets, m.p. 154°.

Anal. Calcd. for $C_{25}H_{26}N_4O_4$: N, 12.6. Found: N, 12.4.

1,2-Diphenyl-2-(4-n-hexylphenyl)ethylene (II). Obtained from 26 g. of the foregoing ketone and an ethereal solution of benzyl magnesium chloride prepared from 20 g. of benzyl chloride and 4 g. of magnesium, this *hydrocarbon* was a pale yellow, viscous oil, b.p. 280–281°/20 mm., n_D^{24} 1.6109. Yield: 30 g.

Anal. Calcd. for $C_{26}H_{28}$: C, 91.7; H, 8.3. Found: C, 91.8; H, 8.2.

1-Bromo-1,2-diphenyl-2-(4-n-hexylphenyl)ethylene (V). Prepared from 10.2 g. of the foregoing ethylene and 4.8 g. of bromine in chloroform, this *compound* crystallized from ethanol in fine colorless prisms, m.p. 93°.

Anal. Calcd. for $C_{26}H_{27}Br$: C, 74.5; H, 6.4. Found: C, 74.2; H, 6.3.

1,2-Diphenyl-2-(4-ethylphenyl)acrylonitriles (VI). To a solution of 12 g. of benzyl cyanide in 250 ml. of anhydrous ether, 8 g. of finely powdered sodium amide was added in small portions, and the mixture refluxed for 15 min. on the water bath. After cooling, 25 g. of 4-ethylbenzophenone was added portionwise, and the mixture refluxed for six more hours. After decomposition with ice and acidification with acetic acid, the ethereal layer was washed with water and dried over sodium sulfate. The solvent was distilled off and the residue vacuum-fractionated. The portion boiling at 275°/18 mm. yielded on recrystallization from acetic acid the *first isomer*, in the form of fine, shiny, colorless prisms, m.p. 130°. Yield: 9 g.

Anal. Calcd. for $C_{23}H_{19}N$: C, 89.3; H, 6.2. Found: C, 89.2; H, 6.4.

Concentration of the mother liquors gave an oil which solidified on prolonged standing; repeated crystallization from acetic acid afforded the *isomeric compound* (1 g.) in the form of fine colorless prisms, m.p. 111°. The melting point of this compound was depressed on admixture with the foregoing isomer. Both isomers gave a violet coloration with hot sulfuric acid.

Anal. Calcd. for $C_{23}H_{19}N$: C, 89.3; H, 6.2. Found: C, 89.5; H, 6.3.

1-(2,5-Dimethylphenyl)-2-phenyl-2-(4-ethylphenyl)acrylonitrile (VII). This compound was similarly prepared from 5 g. of 4-ethylbenzophenone, 5.5 g. of 2,5-dimethylbenzyl cyanide, and 3 g. of sodium amide in anhydrous ether. The portion boiling at 280°/15 mm. yielded on recrystallization

(7) Huang-Minlon, *J. Am. Chem. Soc.*, 68, 2478 (1946).

from acetic acid only one isomer, in the form of fine colorless prisms, m.p. 138°, giving a violet coloration in hot sulfuric acid. Yield: 3.5 g.

Anal. Calcd. for $C_{25}H_{23}N$: C, 89.0; H, 6.9; N, 4.2. Found: C, 89.2; H, 6.6; N, 4.0.

1-(4-Bromophenyl)-2-phenyl-2-(4-isopropylphenyl)acrylonitrile (VIII). Prepared from 9 g. of 4-isopropylbenzophenone, 9.5 g. of 4-bromobenzyl cyanide, and 5 g. of sodium amide, this product, b.p. 298–300°/13 mm., crystallized from acetic acid in fine colorless prisms, m.p. 148°.

Anal. Calcd. for $C_{24}H_{20}BrN$: C, 71.6, H, 5.0; N, 3.5. Found: C, 71.3; H, 5.0; N, 3.3.

1-(4-Bromophenyl)-2-(2-chlorophenyl)-2-(4-xenyl)acrylonitrile (IX). Prepared from 8 g. of 2-chloro-4′-phenylbenzophenone, 8 g. of 4-bromobenzyl cyanide, and 5 g. of sodium amide, this product crystallized from acetic acid in fine colorless needles, m.p. 210°.

Anal. Calcd. for $C_{27}H_{17}BrClN$: C, 68.9; H, 3.6; N, 3.0. Found: C, 68.6; H, 3.4; N, 2.8.

1-(4-Chlorophenyl)-2-(2-chlorophenyl)-2-(4-xenyl)acrylonitrile (X). This compound was prepared from 10 g. of 2-chloro-4′-phenylbenzophenone, 9 g. of 4-chlorobenzyl cyanide, and 4.2 g. of sodium amide; the portion boiling at 325–328°/13 mm. crystallized from acetic acid in colorless leaflets, m.p. 201°, giving a violet coloration in hot sulfuric acid.

Anal. Calcd. for $C_{27}H_{17}Cl_2N$: C, 76.1; H, 4.0; N, 3.3. Found: C, 75.8; H, 3.8; N, 3.0.

PARIS (VE), FRANCE

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, M.R. SCIENCE INSTITUTE, GUJARAT COLLEGE]

Chalcones and Related Compounds Derived from 2-Hydroxy-5-acetaminoacetophenone II. Flavones and Flavonols

A. A. RAVAL AND N. M. SHAH[1]

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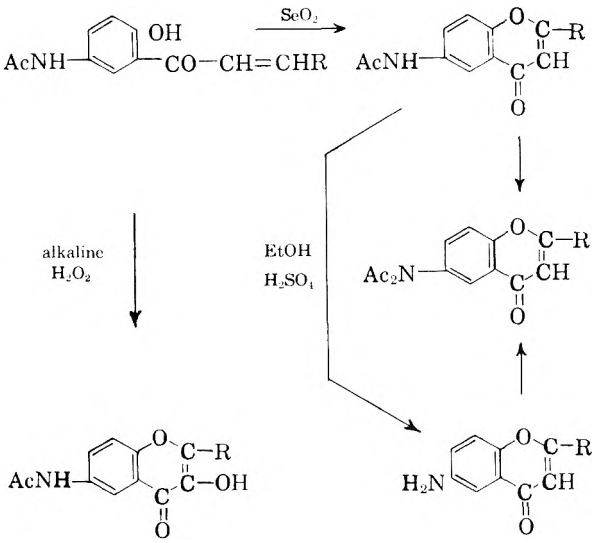
The selenium dioxide oxidation and Algar-Flynn oxidation of some acetaminochalcones derived from 2-hydroxy-5-acetaminoacetophenone have been studied. 6-Acetaminoflavones and flavonols have been synthesized. The 6-acetaminoflavones have been deacetylated by means of ethanolic sulfuric acid, the corresponding 6-aminoflavones being obtained.

In a previous paper[2], the authors have described various chalcones derived from 2-hydroxy-5-acetaminoacetophenone by condensing it with various aldehydes and the chalcones obtained have been cyclized to the corresponding 6-aminoflavanones. The work has now been extended to the synthesis of other heterocyclic compounds, and the synthesis of 6-aminoflavones and 6-acetaminoflavanols from the above chalcones is described in this paper.

When the acetaminochalcones were subjected to selenium dioxide oxidation,[3] 6-acetaminoflavones were obtained, which on deacetylation by ethanolic sulfuric acid, gave the corresponding 6-aminoflavones.

The chalcones were then subjected to Algar-Flynn oxidation[4] using alkaline hydrogen peroxide. Under these conditions, the corresponding 6-acetaminoflavonols were obtained.

Neither selenium dioxide nor Algar-Flynn oxidation of 2,2′-dihydroxy-5′-acetaminochalcone succeeded.



R = C_6H_5; *p*-$C_6H_4OCH_3$; 3,4-$C_6H_3(CH_2O_2)$; *m*-C_6H_4OH.

EXPERIMENTAL

6-Acetaminoflavone. A mixture of 2′-hydroxy-5′-acetaminochalcone (0.5 g.) and selenium dioxide (0.5 g.) in dry isoamyl alcohol (15 ml.) was refluxed on an oil bath at 160–170° for 12 hr. The reaction mixture was then filtered while hot to remove precipitated selenium, and the filtrate was steam-distilled to remove isoamyl alcohol. A dark brown solid, along with some pasty mass, separated; this was filtered, dried, and extracted with benzene; the solid obtained after the removal of benzene was recrystallized twice from ethanol, producing yellowish brown needles, m.p. 174°. Yield, 0.3 g.

Anal. Calcd. for $C_{17}H_{13}O_3N$: C, 73.12; H, 4.66; N, 5.02. Found: C, 73.05; H, 4.47; N, 4.48.

It is soluble in ethanol, acetic acid, benzene, and chloroform. It gives greenish fluorescence with concentrated H_2SO_4. It does not give the $FeCl_3$ color test. It is insoluble in dilute alkali and dilute hydrochloric acid.

The *diacetyl* derivative prepared by the acetic anhydride-

(1) Present address, Department of Chemistry, St. Xavier's College, Ahmedabad-6.

(2) A. A. Raval and N. M. Shah, *J. Org. Chem.*, **21**, 1408 (1956).

(3) K. Venkataraman *et al.*, *J. Chem. Soc.*, 866 (1935); 569 (1936).

(4) J. Algar and J. Flynn, *Proc. Roy. Irish Acad.*, **B 42**, 1 (1934).

pyridine method, crystallized from ethanol as brown granules, m.p. 256–258°.

Anal. Calcd. for $C_{19}H_{15}O_4N$: N, 4.36. Found: N, 4.03.

Deacetylation: formation of 6-aminoflavone. To a solution of 6-acetaminoflavone (0.5 g.) in ethanol (25 ml.), dilute sulfuric acid (10%; 20 ml.) was added gradually until a slight turbidity resulted. The turbidity was removed by adding more ethanol. The clear solution was refluxed on a water bath for 6 hr. The excess of ethanol was then distilled and the remaining liquor was treated with ammonia until it became alkaline. Excess of ammonia was expelled by heating the mixture on a water bath for 15 min. The brown solid was collected, washed with water, and crystallized from ethanol as brown needles, m.p. 192°. Yield, 0.2 g.

Anal. Calcd. for $C_{15}H_{11}O_2N$: C, 76.0; H, 4.64; N, 5.90. Found: C, 75.91; H, 4.52; N, 5.57.

It is soluble in ethanol, acetic acid, ethyl acetate, and benzene. It dissolves in concentrated H_2SO_4 with a blue fluorescence. It is insoluble in dilute alkali, but dissolves readily in dilute mineral acids. It does not give a $FeCl_3$ color test. The *diacetyl* derivative crystallized from ethanol as brown granules, m.p. 256–258°; a mixed melting point with the sample described earlier remained undepressed.

The following flavones were similarly prepared from different chalcones. To avoid repetition, the experimental details are omitted.

The compound *6-acetamino-4′-methoxyflavone* was prepared from 2′-hydroxy-5′-acetamino-4-methoxychalcone. It crystallized from benzene as light brown needles, m.p. 255°.

Anal. Calcd. for $C_{18}H_{15}NO_4$: C, 69.90; H, 4.85; N, 4.53. Found: C, 69.45; H, 4.40; N, 4.18.

It is soluble in ethanol, acetic acid, benzene, and chloroform. It is insoluble in dilute alkali as well as in dilute mineral acids. It dissolves with a yellowish brown color in concentrated H_2SO_4, the solution exhibiting violet fluorescence.

The *diacetyl* derivative prepared by the acetic anhydride-sodium acetate method, crystallized from ethanol as deep yellow granules, m.p. 270°.

Anal. Calcd. for $C_{20}H_{17}NO_5$: N, 3.98. Found: N, 3.68.

6-Amino-4′-methoxyflavone. The compound 6-acetamino-4′-methoxyflavone was deacetylated by dilute sulfuric acid under the same conditions as described previously. The brown solid was collected, washed with water, and crystallized from ethanol as brown needles, m.p. 147–148°.

Anal. Calcd. for $C_{16}H_{13}NO_3$: C, 71.91; H, 4.87; N, 5.24. Found: C, 71.25; H, 4.65; N, 4.95.

It is soluble in ethanol, acetic acid, ethyl acetate, benzene, and acetone. It dissolves in concentrated H_2SO_4 with greenish-blue fluorescence. It is insoluble in dilute alkali but dissolves readily in dilute mineral acids. On acetylation, it gave the *diacetyl* derivative, m.p. 270°; a mixed melting point with the sample described above remained undepressed.

6-Acetamino-3′,4′-methylenedioxyflavone from 2′-hydroxy-5′-acetamino-3,4-methylenedioxychalcone crystallized from ethanol as brownish needles, m.p. 130°.

Anal. Calcd. for $C_{18}H_{13}NO_5$: C, 66.88; H, 4.02; N, 4.33. Found: C, 66.50; H, 3.91; N, 3.99.

It is soluble in ethanol, ethyl acetate, acetic acid, benzene, and chloroform. It is insoluble in dilute alkali as well as dilute mineral acids. It gives greenish fluorescence with concentrated H_2SO_4.

The *diacetyl* derivative, crystallized from ethanol as a brown powder, m.p. 280°.

Anal. Calcd. for $C_{20}H_{15}NO_6$: N, 3.83. Found: N, 3.50.

6-Amino-3′,4′-methylenedioxyflavone obtained by deacetylating the above flavone as previously described, crystallized from ethanol as a dark brown powder, m.p. 180°.

Anal. Calcd. for $C_{16}H_{11}NO_4$: N, 4.98. Found: N, 4.60.

It is soluble in ethanol, acetic acid, and ethyl acetate. It gives bluish-green fluorescence with concentrated sulfuric acid. It is insoluble in dilute alkali, but it dissolves readily in dilute mineral acids.

The amino-flavone was acetylated: a *diacetyl* derivative identical with the above was obtained, m.p. 280°; a mixed melting point with the same obtained previously remained undepressed.

6-Acetamino-3′-hydroxyflavone from 2′-hydroxy-5′-acetamino-3-hydroxychalcone crystallized from ethanol as brownish needles, m.p. 260°.

Anal. Calcd. for $C_{17}H_{13}NO_4$: N, 4.74. Found: N, 4.45.

It is soluble in ethanol, acetic acid, chloroform, acetone, and benzene. It is insoluble in dilute alkali as well as in dilute mineral acids. It gives a greenish fluorescence with concentrated H_2SO_4.

The *acetyl* derivative, prepared by the acetic anhydride–sodium acetate method, crystallized from ethanol as brown granules, m.p. 270°.

Anal. Calcd. for $C_{21}H_{17}NO_6$: N, 3.69. Found: N, 3.42.

6-Amino-3′-hydroxyflavone obtained by deacetylating 6-acetamino-3′-hydroxyflavone as before, crystallized from ethanol as brown granules, m.p. 300°.

Anal. Calcd. for $C_{15}H_{11}NO_3$: N, 5.53. Found: N, 5.31.

It is soluble in ethanol, acetic acid, and benzene. It is insoluble in dilute alkali but readily dissolves in dilute mineral acids. It gives a pale greenish fluorescence with concentrated H_2SO_4.

The *acetyl* derivative, prepared by the acetic anhydride–sodium acetate method, crystallized from ethanol as brown granules, m.p. 270°, a mixed melting point with the same described before remaining undepressed.

6-Acetaminoflavonol. To an ethanolic solution of 2′-hydroxy-5′-acetaminochalcone (0.5 g. in 20 ml.), sodium hydroxide solution (5%; 20 ml.), was added. The deep red solution was cooled in an ice bath and hydrogen peroxide (16.5%; 5 ml.) was added to it. The reaction mixture was kept in an ice bath for 2 hr. and then left overnight at room temperature, whereupon the color of the mixture turned orange. It was acidified by dilution with ice-cold acidulated water; the solid that separated was filtered, washed with water, and crystallized from acetic acid as pale yellow thick plates, m.p. 278°. Yield, 0.2 g.

Anal. Calcd. for $C_{17}H_{13}NO_4$: C, 69.15; H, 4.40; N, 4.74. Found: C, 69.02; H, 4.32; N, 4.63.

It is soluble in excess of dilute alkali, but insoluble in dilute hydrochloric acid. It is soluble in acetic acid, chloroform, acetone and sparingly soluble in ethanol and ethyl acetate. It gives a violet fluorescence with concentrated sulfuric acid.

The following flavonols were similarly prepared from different chalcones. To avoid repetition, the experimental details are omitted.

6-Acetamino-4′-methoxyflavonol was obtained from 2-hydroxy-5′-acetamino-4-methoxychalcone and crystallized from acetic acid as light yellow long needles, m.p. 257°.

Anal. Calcd. for $C_{18}H_{15}NO_5$: C, 66.45; H, 4.61; N, 4.30. Found: C, 66.50; H, 4.45; N, 4.03.

It is insoluble in ethanol and dilute hydrochloric acid, but dissolves in excess of dilute caustic alkali. It gives a green fluorescence when dissolved in concentrated sulfuric acid and a bluish-green fluorescence with Wilson's[5] boric acid reagent.

6-Acetamino-3′,4′-methylenedioxyflavonol from 2′-hydroxy-5′-acetamino-3,4-methylenedioxychalcone crystallized from acetic acid as pale yellow granules, m.p. 272–273°.

Anal. Calcd. for $C_{18}H_{13}NO_6$: C, 63.73; H, 3.84; N, 4.13. Found: C, 63.50; H, 3.44; N, 3.78.

It is soluble in acetic acid, chloroform, and acetone, but sparingly soluble in ethanol and ethyl acetate. It gives a bluish, violet fluorescence with concentrated sulfuric acid. It is soluble in excess of dilute alkali but is insoluble in dilute mineral acids.

6-Acetamino-3′-hydroxyflavonol was obtained from 2′-hydroxy-5′-acetamino-3-hydroxychalcone and crystallized from acetic acid as pale yellow leaflets, m.p. >300°.

(5) C. W. Wilson, *Chem. Soc.*, 61, 2303 (1939).

Anal. Calcd. for $C_{17}H_{11}NO_6$: C, 65.59; H, 4.18; N, 4.50. Found: C, 65.21; H, 4.00; N, 4.30.

It is soluble in acetic acid, chloroform, and acetone. It is insoluble in dilute mineral acids. It gives a greenish-blue fluorescence with concentrated sulfuric acid.

The deacetylation of these flavonols was not successful either with sulfuric acid or with anhydrous aluminum chloride.

AHMEDABAD-6 (INDIA)

[CONTRIBUTION FROM THE LABORATORY FOR THE STUDY OF HEREDITARY AND METABOLIC DISORDERS AND THE DEPARTMENTS OF BIOLOGICAL CHEMISTRY AND MEDICINE, UNIVERSITY OF UTAH COLLEGE OF MEDICINE]

Preparation of 5-Hydroxy-L- and D-Tryptophan[1]

ALLAN J. MORRIS AND MARVIN D. ARMSTRONG

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5-Hydroxy-DL-tryptophan has been resolved by fractional crystallization of the quinine salts of N-carbobenzoxy-5-benzyloxy-DL-tryptophan. Configurations have been assigned to the resolved isomers, and 5-hydroxy-L- and D-tryptophan have been obtained by catalytic hydrogenation of N-carbobenzoxy-5-benzyloxy-L- and D-tryptophan, respectively.

Considerable interest has developed in the metabolism of 5-hydroxyindole compounds following the identification of serotonin[2] and enteramine[3] as 5-hydroxytryptamine (5HTA). DL-Tryptophan labelled with carbon-14 has been shown to be converted to 5-hydroxytryptophan (5HT) in the salivary glands of the toad *Bufo Marinus*,[4] tryptophan is converted to 5HT in *Chromobacterium violaceum*[5,6] and a specific decarboxylase which converts 5HT to 5HTA is present in the kidney tissue of dogs and guinea pigs.[7] Thus, 5-hydroxytryptophan appears to be a naturally occurring amino acid of considerable physiological importance.

Significant differences have been reported in the metabolism of the D- and the L- forms of many amino acids *in vivo*, particularly the aromatic amino acids. The administration of DL-phenylalanine leads to the excretion of phenylpyruvic acid,[8] whereas L-phenylalanine appears to be completely metabolized by infants.[9] D-Tryptophan is to some extent excreted unchanged[10] and is in part converted to indolelactic and indoleacetic acids,[11] whereas L-tryptophan is more completely metabolized by the human.[12] L-DOPA is converted in large part to homoprotocatechuic and homovanillic acids whereas D-DOPA is in part excreted unchanged and a considerable portion of the amount administered remains unaccounted for in the human.[13] Because of the natural occurrence of 5-hydroxytryptophan and because of the desirability of conducting both *in vivo* metabolic experiments and *in vitro* enzymatic studies with pure optical isomers, the resolution of this amino acid was undertaken.

Preliminary attempts to resolve 5-hydroxytryptophan as the N-formyl derivative were unsuccessful. The N-acetyl derivative was considered even less suitable because of difficulties encountered in hydrolyzing the compound in preliminary studies. N-Carbobenzoxy-5-benzyloxy-DL-tryptophan was then prepared and was resolved by fractional crystallization of the quinine salts from a benzene solution. Catalytic hydrogenation of the N-carbobenzoxy-5-benzyloxy-D- and L-tryptophans afforded 5-hydroxy-D-tryptophan and 5-hydroxy-L-tryptophan, respectively. The yield of 5-hydroxy-L-tryptophan from N-carbobenzoxy-5-benzyloxy-DL-tryptophan was 42%. Configuration of the respective antipodes was established by comparison of the rotation of the resolved isomers with those of tryptophan, by the shift in optical rotation of the L- isomer to a more positive value in acid solution[14] and by the papain-catalyzed formation of N-carbobenzoxy-5-benzyloxy-L-tryptophan anilide.[15]

EXPERIMENTAL

N-Carbobenzoxy-5-benzyloxy-DL-tryptophan. 5-Benzyloxy-DL-tryptophan[16,17] (20.0 g., 0.064 mole) was suspended in a

(1) This work was supported by research grants from the National Institutes of Health, United States Public Health Service.

(2) Rapport, *J. Biol. Chem.*, **180**, 961 (1949).

(3) Erspamer and Asero, *Nature*, **169**, 800 (1952).

(4) Mitoma, Weissbach, and Udenfriend, *Nature*, **175**, 994 (1955).

(5) Mitoma, Weissbach, and Udenfriend, *Arch. Biochem. Biophys.*, **63**, 122 (1956).

(6) Udenfriend, Titus, Weissbach, and Peterson, *J. Biol. Chem.*, **219**, 335 (1956).

(7) Udenfriend, Clark and Titus, *J. Am. Chem. Soc.*, **75**, 501 (1953).

(8) Levine, Marples, and Gordon, *J. Clin. Invest.*, **20**, 199 (1941).

(9) Woolf and Edmunds, *Biochem. J.*, **47**, 630 (1950).

(10) Langner and Berg, *J. Biol. Chem.*, **214**, 699 (1955).

(11) Armstrong and Robinson, *Arch. Biochem. Biophys.*, **52**, 287 (1954).

(12) Sarett and Goldsmith, *J. Biol. Chem.*, **182**, 679 (1950).

(13) Shaw, McMillan, and Armstrong, *Federation Proc.*, **15**, 353 (1956).

(14) Lutz and Jirgensons, *Ber.*, **63**, 448 (1930); **64**, 1221 (1931).

(15) Hanson and Smith, *J. Biol. Chem.*, **179**, 815 (1949).

(16) Ek and Witkop, *J. Am. Chem. Soc.*, **76**, 5579 (1954).

(17) We wish to express our appreciation to the Upjohn Company for the gift of a generous supply of 5-benzyloxyindole.

solution of 2.60 g. of NaOH in 450 ml. of water and cooled to 0° in a freezing mixture. In five equal portions, over a period of 80 min., was added 12.2 ml. (0.072 mole) of carbobenzoxy chloride and 72 ml. of 1*N* sodium hydroxide (temperature was maintained at −5° and *p*H at 10); the mixture was shaken thoroughly after each addition. The resulting solution was maintained at 0° for 30 min. and was then allowed to warm to room temperature slowly. The solution was extracted once with ether, and the aqueous phase was acidified to *p*H 1.5 with HCl and was extracted with three 250-ml. portions of EtOAc. The combined EtOAc extracts were dried over anhydrous Na_2SO_4 at 5°, treated with charcoal, filtered, and the solvent was removed *in vacuo*. The resulting oil, which partially crystallized, was dissolved in 650 ml. of boiling benzene, and the solution was filtered and cooled to 10° for 30 min. The product was collected, washed with cold benzene, and dried; 23.2 g. (81%), m.p. 132–133°.[18] For analysis, a portion was recrystallized from benzene, m.p. 133–134°.

Anal.[19] Calcd. for $C_{26}H_{24}N_2O_5$: C, 70.25; H, 5.44; N, 6.30. Found: C, 71.09; H, 5.33; N, 6.16.

*Resolution of N-Carbobenzoxy-5-benzyloxy-*DL*-tryptophan.* Carbobenzoxy-5-benzyloxy-DL-tryptophan (47.5 g.) and anhydrous quinine (34.8 g.) were dissolved in 750 ml. of boiling benzene. To promote crystallization, the solution was heated to boiling and cooled three times during a period of 1 hr. The suspension was allowed to stand overnight at room temperature and the crystalline precipitate was collected on a filter, washed with a small volume of benzene and dried *in vacuo;* crop A, 44.4 g., m.p. 136–138°. Crop A was slurried with 500 ml. of benzene, simmered for several minutes and filtered while hot to yield 37.9 g. of white crystalline solid, m.p. 138–140°. The filtrate was cooled to room temperature and yielded an additional 2.0 g., m.p. 137–138°. The two fractions were combined to form crop B, $[\alpha]_D^{22}$ −83.9° (c 1, abs. EtOH). Crop B was simmered with 500 ml. of benzene for 30 min. and filtered to yield crop C; 37.3 g., m.p. 141–142°, $[\alpha]_D^{22}$ −85.8 (c 1, abs. EtOH). Crop C was dissolved in a boiling mixture of 2 l. of benzene and 400 ml. of absolute methanol, filtered, and concentrated *in vacuo* until crystallization commenced. The solution was allowed to stand overnight at room temperature, and was cooled to 10° for 30 min. and filtered to yield 33.8 g. of crop D; $[\alpha]_D^{22}$ −86.9° (c 1, abs. EtOH). Crop D was recrystallized in a similar manner from a boiling mixture of 3 l. of benzene and 60 ml. of abs. EtOH to yield crop E; 30.7 g., m.p. 143–144°, $[\alpha]_D^{22}$ −91.1° (c 1, abs. EtOH). Recrystallization of crop E from a boiling mixture of 4 l. of benzene and 30 ml. of abs. EtOH by the same procedure gave 28.3 g. of crop F; m.p. 168–169° (marked shrinkage at 145°), $[\alpha]_D^{22}$ −92.1 (c 1, abs. EtOH). Recrystallization of crop F in the same manner gave 22.5 g. of crop G, m.p. 145–146°, $[\alpha]_D^{22}$ −94.3° (c 1, abs. EtOH). Further recrystallization did not lead to any further change in the rotation of the salt.

Crop G was suspended in a mixture of 250 ml. of water and 150 ml. of ethyl acetate, and 6*N* HCl was added to the stirred mixture until the *p*H of the aqueous phase was 1.5. The EtOAc was separated and the aqueous phase was extracted two more times with 100 ml. portions of ethyl acetate. The combined ethyl acetate extracts were washed with several small portions of dilute HCl (*p*H 1.5) to remove the last traces of quinine. The extracts were dried over anhydrous Na_2SO_4, treated with charcoal, filtered, and the solvent was removed *in vacuo*. The residue was dissolved in a minimum volume of hot benzene, left at room temperature overnight, and then cooled to 10° for 1 hr. The crystalline product was collected on a filter and dried *in vacuo;* 12.6 g. of N-carbobenzoxy-5-benzyloxy-D-tryptophan (97% yield from salt), m.p. 97–99°, $[\alpha]_D^{22}$ +10.3° (c 1, abs. EtOH). For analysis, a portion was recrystallized three times from hot benzene; m.p. 98–99°.

Anal. Calcd. for $C_{26}H_{24}N_2O_5$: C, 70.25; H, 5.44; N, 6.30. Found: C, 70.28; H, 5.32; N, 6.05.

When the filtrate from crop A was heated to boiling and cooled, further crystallization occurred; 18.8 g. (m.p. 157–158°) of salt was collected. This procedure was repeated on the filtrate and another 11.2 g. (m.p. 156–157°) was obtained. These two fractions were combined as crop H. Crop H was combined with the filtrate from crop B and dissolved in a total volume of 4.75 l. of boiling benzene. The solution was left overnight at room temperature, cooled to 10° for several hours and the crystals which had formed were collected on a filter, washed with cold benzene, and dried *in vacuo;* 7.6 g. of quinine salt was obtained, m.p. 159–160°. The filtrate was concentrated to a volume of 3 l. and a further 20.9 g. of quinine salt, m.p. 157–158°, was thus obtained. These two fractions were combined to form crop I; $[\alpha]_D^{22}$ −35.1° (c 1, abs. EtOH). Crop I was dissolved in 3.6 l. of boiling benzene and crop J was collected after 24 hr. at room temperature; 17.7 g., m.p. 158–159°, $[\alpha]_D^{22}$ −33.3° (c 1, abs. EtOH). Another crop (K) was collected from the same solution after another 24 hr.; 3.0 g., m.p. 157–158°, $[\alpha]_D^{22}$ −32.5° (c 1, abs. EtOH). Crop J was recrystallized from 2.25 l. of boiling benzene to yield 13.7 g. of crop L (m.p. 160–161°), $[\alpha]_D^{22}$ −32.9° (c 1, abs. EtOH), which was combined with crop K and again recrystallized to yield 14.9 g. of crop M; m.p. 160°, $[\alpha]_D^{22}$ −32.4° (c 1, abs. EtOH). Further recrystallization did not lead to a change in the rotation of the salt. Quinine was removed in the manner described for the other isomer; 8.4 g. of *N*-carbobenzoxy-5-benzyloxy-L-tryptophan (98% yield from salt), m.p. 97–99°, $[\alpha]_D^{22}$ −10.1° (c 1, abs. EtOH). For analysis, a small sample was recrystallized from benzene; m.p. 97–99°.

Anal. Calcd. for $C_{26}H_{24}N_2O_5$: C, 70.25; H, 5.44; N, 6.30. Found: C, 70.11; H, 5.33; N, 6.35.

The filtrates from crops I–M were combined and concentrated to a small volume, treated with charcoal, filtered, and fractionated as described above, to provide additional quinine salt from which 4.3 g. of N-carbobenzoxy-5-benzyloxy-L-tryptophan was obtained (total yield, 12.7 g.).

*N-Carbobenzoxy-5-benzyloxy-*L*-tryptophan anilide.* To a mixture of 30 mg. of N-carbobenzoxy-5-benzyloxy-L-tryptophan, 0.6 ml. of 0.05 *M* 2,3-dimercaptopropanol, 5 ml. of 0.1*M* *p*H 5.2 citrate buffer, and 0.13 ml. of aniline was added 4 mg. of crystalline mercuripapain[20] and the mixture was incubated at 39° for 3 days. The reaction mixture was filtered and the product was washed through the filter with small portions of 0.1*N* hydrochloric acid. The combined filtrate and acid washes were adjusted to *p*H 11.5 and extracted with ether for 20 hr. in a continuous extractor. The ether extract was concentrated to dryness and the residual solid was recrystallized from abs. EtOH to yield 16 mg. of white needles, m.p. 187°.

Anal. Calcd. for $C_{32}H_{29}N_3O_4$: N, 8.09. Found: N, 7.76.

The aqueous phase from the ether extraction was acidified to *p*H 1.5 and was extracted with ethyl acetate. No N-carbobenzoxy-5-benzyloxy-L-tryptophan could be recovered.

N-Carbobenzoxy-5-benzyloxy-D-tryptophan (30 mg.) was treated by the same procedure. No anilide was obtained but 18 mg. of N-carbobenzoxy-5-benzyloxy-D-tryptophan (m.p. 98–99°) was recovered.

*5-Hydroxy-*L*-tryptophan.* Palladium oxide (300 mg.) was added to a solution of 2.0 g. of N-carbobenzoxy-5-benzyloxy-L-tryptophan in 150 ml. of abs. EtOH and 1 ml. of water, and hydrogen was bubbled through the mixture for 3 hr. The precipitate which formed was dissolved by the addition of hot water and the solution was filtered under nitrogen. The filtrate was concentrated to dryness *in vacuo* under nitrogen and washed with ethyl acetate to remove

(18) Melting points were taken in open capillary tubes and are uncorrected.

(19) Analyses were performed by the Weiler and Strauss Microanalytical Laboratory, Oxford, England.

(20) We are indebted to Drs. J. R. Kimmel and E. L. Smith of this Laboratory for the mercuripapain used in this procedure.

starting material. The remaining solid was dissolved in a minimium volume (about 4 ml.) of hot water under nitrogen, treated with charcoal, filtered under nitrogen, and allowed to crystallize at 5°. 5-Hydroxy-L-tryptophan was recovered as pale pink needles; 0.55 g., m.p. 273° dec., $[\alpha]_D^{22}$ −32.5° (c 1, water), $[\alpha]_D^{22}$ +16.0° (c 1, 4*N* HCl) (L-tryptophan, $[\alpha]_D^{23}$ −31.5° (c 1, water).[21] The filtrate was concentrated to yield an additional 0.11 g. In this manner, a total of 4.7 g. of 5-hydroxy-L-tryptophan (80% theor.) was obtained from 12.0 g. of N-carbobenzoxy-5-benzyloxy-L-tryptophan.

A sample was prepared for analysis by recrystallization from water under nitrogen.

Anal. Calcd. for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.65; H, 5.44; N, 12.50.

5-Hydroxy-D-tryptophan. N-Carbobenzoxy-5-benzyloxy-D-tryptophan (2.0 g.) was reduced by the procedure described for the L-isomer to yield 0.60 g. (61% yield) of 5-hydroxy-D-tryptophan; m.p. 274° dec., $[\alpha]_D^{22}$ +32.2° (c 1, water).

A sample was prepared for analysis by recrystallization from water under nitrogen.

Anal. Calcd. for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.86; H, 5.62; N, 12.50.

5-Hydroxy-L-tryptophan picrolonate. 5-Hydroxy-L-tryptophan (30 mg.) and 36 mg. of picrolonic acid were dissolved in 3 ml. of hot water under nitrogen. The yellow needles which formed on cooling were collected on a filter; 54 mg. (82% yield), m.p. 184–186° (dec.). For analysis, a portion was recrystallized three times from hot water, m.p. 184–186° (dec.).

Anal. Calcd. for $C_{21}H_{20}N_6O_8 \cdot H_2O$: C, 50.19; H, 4.41; N, 16.74. Found: C, 50.45; H, 4.57; N, 17.00.

SALT LAKE CITY, UTAH

(21) Greenberg, *Chemistry of the Amino Acids and Proteins*, C. C. Thomas, Springfield, Ill., 1945, p. 1177.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES DIVISION, NATIONAL DAIRY PRODUCTS CORPORATION]

Potential Antimicrobial Agents. I. Alkyl 4-Oxo-2-alkenoates

HENRY M. WALTON

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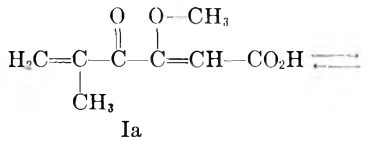
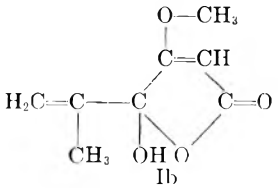
Alkyl 4-oxo-2-alkenoates were conveniently obtained by the retrogressive Diels-Alder reaction of their cyclopentadiene adducts. The requisite adducts were prepared through the interaction of alkylzinc chlorides and half ester chlorides of bicyclo-[2.2.1]5-heptene-2,3-dicarboxylic acid. The analogous reactions were also effected with anthracene adducts.

The structural elucidation of the antibiotic, penicillic acid (Ia, Ib)[1] and its synthesis[2] have

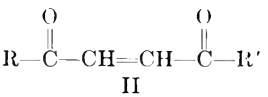


Ia



Ib

stimulated considerable interest in the antimicrobial activity associated with related classes of compounds, notably 4-oxo-2-alkenoic acids (IIa) and certain of their derivatives (IIb, c)



II

R = alkyl, aryl
IIa: R′ = OH
IIb: R′ = alkoxy
IIc: R′ = NH_2, NHR

This interest has focused mainly on β-aroylacrylic acids (IIa)[3a] and their derivatives, esters (IIb)[3b] and amides (IIc),[3c] since the availability of relatively convenient preparative methods in this area was conducive to their examination.

In pronounced contrast there is a lack of adequate preparative methods for the corresponding *aliphatic* analogs of penicillic acid, 4-oxo-2-alkenoic acids, and their derivatives. As a result the antimicrobial properties of but a few compounds of this type have been investigated. Esters of β-acetylacrylic acid[3b,4] and ethyl 4-oxo-2-hexenoate[5] have been shown to have good *in vitro* activity against a number of microorganisms.

Preparatively the esters of β-acetylacrylic acid constitute a special case due to their ready availability from levulinic acid.[6] Ethyl 4-oxo-2-hexe-

(1) T. H. Birkinshaw, A. E. Oxford, and H. Raistrick, *Biochem. J. London*, **30**, 394 (1936). Antibiotic activity: *cf.* references in Baron, *Handbook of Antibiotics*, Reinhold Publishing Corp., New York, 1950, p. 183.

(2) R. A. Raphael, *Nature*, **160**, 261 (1947).

(3a) B. J. Cramer, Wm. J. Moran, C. H. Nield, M. Edwards, Ch. I. Jarowski, and B. Puetzer, *J. Am. Pharm. Assoc. Sci. Ed.*, **37**, 439 (1948). D. Papa and E. Schwenk, U. S. Patent 2,562,208 [*Chem. Abstr.*, **46**, 2759 (1952)]; F. H. Kirchner, J. H. Bailey, and Ch. J. Cavallito, *J. Am. Chem. Soc.*, **71**, 1210 (1949).

(3b) R. L. Worral, Med. World Jan. 11, 1946; J. C. Thomas, U. S. Patent 2,532,579 [*Chem. Abstr.*, **45**, 1290 (1950)].

(3c) B. J. Cramer *et al.* (3a).

(4) See also S. Raymond, *J. Am. Chem. Soc.*, **72**, 4304 (1950).

(5) J. S. Mofatt, G. Newberry, and W. Webster, *J. Chem. Soc.*, 451 (1946).

(6) W. G. Overend, J. M. Turton and L. F. Wiggins, *J. Chem. Soc.*, 3500 (1950): Ethyl 4-oxo-2-pentenoate from ethyl levulinate in two steps and 45% over-all yield.

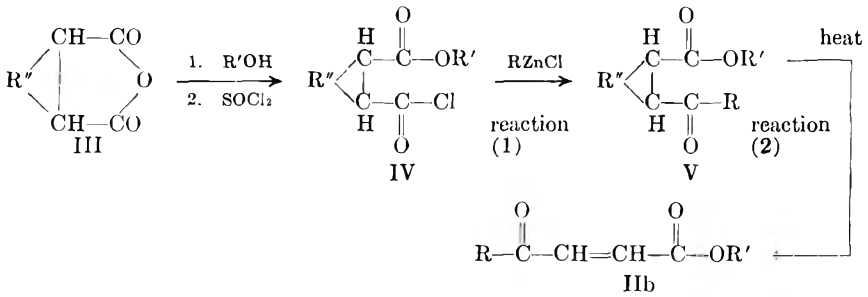
noate has been obtained from the silver salt of the acid by reaction with ethyl iodide.[5] The silver salt–alkyl iodide method may be considered a general one for the preparation of alkyl 4-oxo-2-alkenoates. However, the requisite 4-oxo-2-alkenoic acids remain relatively inaccessible. Mofatt and coworkers[5] devised three interesting methods for the preparation of 4-oxo-2-hexenoic acid which are probably capable of generalization. Subsequently Keskin[7] developed two general methods for the preparation of these acids. Unfortunately, all of these methods are laborious and result in poor over-all yields. The usefulness of the silver salt–alkyl iodide method is thereby severely limited.[8]

For these reasons further investigation of aliphatic analogs for penicillic acid appeared to require additional preparative methods. This paper deals with a new and apparently general method for the preparation of alkyl 4-oxo-2-alkenoates.

Much of the difficulty encountered in the construction of 4-oxo-2-alkenoic esters resides in their ethylenic double bond. When present in a starting material in conjugation with a carbonyl or ester group, its location militates against the employment of convenient methods which might otherwise be used to effect the desired variations in the radical R of structure II. On the other hand, in using saturated starting materials one cannot usually introduce this bond in a convenient and unequivocal manner.

In the present instance this difficulty was overcome by the use of Diels-Alder adducts of maleic anhydride with cyclopentadiene and anthracene, whose propensity for retrogression at elevated temperatures is well known.[9] These adducts were transformed into the corresponding adducts of 4-oxo-2-alkenoates which underwent the expected retrogression at elevated temperatures with the liberation of alkyl 4-oxo-2-alkenoates.[10] Attempts to effect this reaction sequence with furan adducts were unsuccessful.

The reaction sequence is represented as follows:



R″ = 3,5-cyclopenteno- or 9,10-anthraceno-.

In preliminary work this reaction sequence was studied with adducts of maleic anhydride with cyclopentadiene, anthracene, and furan. The crude ester chlorides (IV) resisted all attempts at purification by crystallization or distillation and were used as such. Reaction 1 failed with furan adducts. Complex reaction mixtures were obtained which, undoubtedly, derived in part from the attack of the ester chloride group, in the presence of magnesium chloride and/or zinc chloride, upon the allylic ether oxygen of the furan adducts. Reaction 1 was successful with cyclopentadiene and with anthracene adducts. The use of cyclopentadiene adducts, however, appeared to be conducive to better overall yields. Accordingly they were used in most cases.

The expected thermal instability of cyclopentadiene adducts (V) became apparent during their distillation. Even under 1-mm. pressure most members of the series distilled with varying degrees of retrogression; those having a molecular weight 306 or higher underwent complete retrogression when their distillation was attempted. The presence of alkyl 4-oxo-2-alkenoates in the distillates of their adducts (V) was reflected by analyses and in some cases confirmed by isolation. Table I lists distilled products of reaction 1 which, from their analyses, are inferred to consist wholly or predominantly of keto ester adducts (V).

When desired, the retrogressive Diels-Alder reaction 2 was effected at 180–200° under reduced pressure. This pyrolysis was also carried out to advantage with *crude* adducts (V). The method was thereby reduced to a single step based on ester chloride adducts (IV). In the case of methyl esters

(7) F. L. Breusch and H. Keskin, *Arch. Biochem.*, **18**, 305 (1948); H. Keskin, *Rev. fac. sci. univ. Istanbul*, **15A** (1), 54 (1950), *cf. Chem. Abstr.*, **45**, 2904 (1951).

(8) While this work was under way R. E. Bowman and W. D. Fordham, *J. Chem. Soc.*, 3945 (1952), published an elegant new synthesis of ketonic compounds, a variant of which afforded ethyl *trans*-4-oxo-2-heptadecenoate from β-carboethoxyacrylyl chloride and di(2-)pyranyl dodecylmalonate. The authors consider the method to be limited to the preparation of ethyl esters. Attempts at this Laboratory to apply it to the preparation of lower homologs met with little success.

(9) For a discussion of the retrogressive Diels-Alder reaction see M. C. Kloetzel, *Org. Reactions*, **4**, 9 (1948).

(10) A similar reaction sequence resulting in vinyl ketones *via* their anthracene adducts was recently described by Tatsuyo Shono and Ryohei Oda, *J. Chem. Soc. Japan, Ind. Chem. Sect.*, **58**, 276 (1955); *Bull. Inst. Chem. Research Kyoto Univ.*, **33**, 58 (1955) [*Chem. Abstr.*, **50**, 4102, 14681 (1956)].

TABLE I

KETO ESTERS (V). (CYCLOPENTADIENE ADDUCTS)

R	R′	B.P. °C./Mm.	Formula	Analyses[a] C Calcd.	C Found	H Calcd.	H Found
n-C_3H_7	CH_3	102–104/0.4	$C_{13}H_{18}O_3$	70.25	69.80	8.16	8.04
n-C_4H_9	CH_3	122/2	$C_{14}H_{20}O_3$	71.16	71.00	8.53	8.04
i-C_4H_9	CH_3	108/1[b]	$C_{14}H_{20}O_3$	71.16	70.46	8.53	8.21
n-C_4H_9	C_2H_5	128–130/1	$C_{15}H_{22}O_3$	71.97	71.26	8.86	8.61
n-C_4H_9	C_3H_7	139–142/2	$C_{16}H_{24}O_3$	72.69	71.09	9.15	8.68
n-C_5H_{11}	CH_3	133–140/1.2[b]	$C_{15}H_{22}O_3$	71.97	70.51	8.86	8.41
n-C_6H_{13}	CH_3	131–135/1.3[b]	$C_{16}H_{24}O_3$	72.69	71.01	9.15	8.61
n-C_6H_{13}	C_2H_5	142/1.5	$C_{17}H_{26}O_3$	73.34	71.76	9.42	9.01

[a] See Table II for calculated composition of the corresponding 4-oxo-2-alkenoates. [b] Crystalline material deposited in the distillate, isolated and identified as the corresponding methyl 4-oxo-2-alkenoate.

TABLE II

ALKYL 4-OXO-2-ALKENOATES (IIb)

R	R′	B.P. °C./Mm. or M.P. °C.	Formula	Analyses C Calcd.	C Found	H Calcd.	H Found
n-C_4H_9	CH_3O	104–105.5°/9 35–36°[a]	$C_9H_{14}O_3$	63.51	63.49	8.22	7.94
i-C_4H_9	CH_3O	123–127°/28	$C_9H_{14}O_3$	63.51	62.93	8.22	7.92
n-C_4H_9	C_2H_5O	131–134°/15	$C_{10}H_{16}O_3$	65.19	64.51	8.76	8.17
n-C_5H_{11}	CH_3O	48.5°[a]	$C_{10}H_{16}O_3$	65.09	65.09	8.76	9.00
n-C_6H_{13}	CH_3O	52°[a]	$C_{11}H_{18}O_3$	66.64	66.40	9.15	8.86
cyclo-C_6H_{11}	CH_3O	56–57°[b]	$C_{11}H_{16}O_3$	67.32	66.99	8.22	7.63
n-C_6H_{13}	C_2H_5O	157–158°/14	$C_{12}H_{20}O_3$	67.89	67.91	9.50	9.56
n-C_8H_{17}	C_2H_5O	133–141°/1.2	$C_{14}H_{24}O_3$	69.97	68.81	10.07	9.60
n-C_8H_{17}	n-C_3H_7O	149°/1.5	$C_{15}H_{26}O_3$	70.82	71.17	10.29	9.94
$(CH_3)(C_6H_{13})CH$—	CH_3O	105–108°/1	$C_{13}H_{22}O_3$	68.99	69.35	9.80	9.50

[a] Recrystallized from low boiling petroleum ether. [b] Recrystallized from ligroin, b.p. 66–75°.

yields of 30–60% were obtained. Table II lists alkyl 4-oxo-2-alkenoates prepared by the new method.

Methyl 4-oxo-2-octenoate had λ_{max}^{MeOH} 220 mμ, ε 14,500; reported for methyl 4-oxo-2-pentenoate[4] and for methyl *trans*-4-oxo-2-heptadecenoate,[8] λ_{max} 222 mμ.

Positive structure proof for methyl 4-oxo-2-nonenoate prepared by the new method was afforded by comparing it with a specimen obtained from the silver salt of the known 4-oxo-2-nonenoic acid[7] and methyl iodide. The melting points of the esters were: *via* adducts (IV, V), 48°; *via* the silver salt, 46.5°. No melting point depression resulted from their admixture.

EXPERIMENTAL

All melting points were determined on a Fisher-Johns melting point block; the thermometer was calibrated with Keufler "Testsubstanzen." Boiling points are uncorrected.

Half esters of bicyclo[2.2.1]5-heptene-2,3-dicarboxylic acid. (a) Without catalyst. A mixture of bicyclo[2.2.1]5-heptene-2,3-dicarboxylic anhydride (328.4 g., 2.0 moles) and methanol (85 g., 2.65 moles) was heated under reflux. After 2 hr. a clear solution was obtained. Heating was continued for 1 hr. during which the solution attained a temperature of 115°. After cooling to 50°, the solution was seeded. Crystallization was allowed to proceed for several hours at 50° and finally at room temperature. The crystalline mass was slurried with 300 ml. isopropyl ether, filtered with suction, and washed once with 100 ml. isopropyl ether and twice with low boiling petroleum ether. The air-dried material melted at 103.5–105° and weighed 320 g. (yield 82%). By working up the mother liquors, a small amount of additional material (20.5 g.) of m.p. 102–103° was obtained. This represents a modification of the method of L. M. Rice and E. E. Reid[11] who reported the melting point of 102–103°.

(b) With potassium acetate catalyst. A mixture of bicyclo[2.2.1]5-heptene-2,3-dicarboxylic anhydride (164 g., 1.0 mole), methanol (100 g., 3.1 moles) and potassium acetate (1.0 g., 0.01 mole) was warmed briefly on the steam bath with occasional swirling until a clear solution was obtained. When the solution had returned to room temperature it was seeded and allowed to crystallize for several hours. The crystalline mass was filtered with suction, washed carefully with 30 g. methanol, and air-dried. The resulting product represented a yield of 42%. The combined methanolic solutions were used to convert additional anhydride (1.0 mole) into methyl half esters by the same procedure. By repetition of this process, a series of crops was obtained which varied between 0.9 and 1.1 moles of half ester and melted within 1 degree of the reported melting point.[11] With several repetitions and final concentration of the mother liquors on the steam bath, over-all yields exceeding 95% were obtained.

The method is applicable to the preparation of the corresponding ethyl and n-propyl esters. Half esters of furan adducts were obtained similarly.

Bicyclo[2.2.1]5-heptene-2-carbalkoxy-3-carbonylchlorides (IV). The half ester was allowed to react at room tempera-

(11) L. M. Rice and E. E. Reid, *J. Am. Chem. Soc.*, **74**, 3955 (1952).

ture with a 30–40% molar excess of thionyl chloride. The reaction was completed with warming to 40–50° (water bath) during 10–30 min. Volatile components of the mixture were removed under 10–15-mm. pressure at room or slightly elevated temperatures. A small amount of benzene was added to the residue and concentration *in vacuo* was repeated. Almost colorless to light straw-colored noncrystallizing oils were obtained which darkened slowly upon standing. Attempted distillation resulted in regeneration of the anhydride adduct (III) and, presumably, in the formation of alkyl chloride. A small sample of the oil was dissolved in acetone and hydrolyzed by the dropwise addition of water; the neutralization equivalent of the solution was usually found to be about 103% of theory. Yields of ester chloride adducts (IV), calculated on this basis, were 97–100%. High yields of regenerated half esters could be isolated from hydrolysis mixtures.

Furan analogs prepared in this manner darkened much more rapidly.

Methyl bicyclo[2.2.1]5-heptene-3-n-valeryl-2-carboxylate (V). The requisite ester chloride was prepared as above using 250 g. (1.27 moles) of the methyl half ester and 195 g. (1.65 moles) of thionyl chloride. The ester chloride was obtained as a straw-colored oil which weighed 279 g.; its neutralization equivalent was: calcd., 107.3; found, 109. The yield was quantitative.

The preparation of the Grignard reagent, its reaction with zinc chloride, and the condensation with ester chloride were carried out under dry nitrogen by a modification of the method of Jones.[12] An efficient stainless steel stirrer and a Teflon bearing were used.

Stirring was maintained throughout the following operations. A stock solution of 1.74*N* *n*-butylmagnesium chloride (1000 ml.) containing traces of methylmagnesium iodide, was added gradually with stirring to zinc chloride (237 g., 1.74 moles) in ether (about 350 ml.). Following the addition, the mixture was heated under reflux for 1 hr. Ether (700 ml.) was distilled off and benzene (1000 ml.) was added to the distilland. The replacement of ether by benzene was continued by alternate distillation of solvent (750 and 375 ml. of distillate) and replenishment of the distillation residue by equivalent volume of benzene. The final vapor temperature was 75°. The freshly prepared ester chloride, dissolved in 580 ml. benzene, was added gradually, with *vigorous* stirring, to the cooled alkylzinc chloride reagent. By suitable external cooling the temperature of the reaction mixture was kept at 42°. When the addition was completed, the mixture was kept at 40° for 4 hr. It was allowed to cool and stand at room temperature overnight. The mixture was decomposed by the slow addition, with external cooling, of 3*N* hydrochloric acid. The aqueous layer was separated and extracted with benzene. The combined benzene solutions were washed several times wi h water and once with sodium bicarbonate solution. The washed benzene solutions were stirred during several hours with potassium carbonate (50 g.), filtered, and allowed to evaporate at room temperature. Vacuum fractionation of the residue afforded a fore-fraction, b.p. 100–120°/2 mm., a main fraction consisting of a pale yellow oil, b.p. 122°/2 mm. (196 g.), which was followed by a darker yellow oil, b.p. 130°/2 mm.–145°/4 mm. (dec.). A small amount (10.6 g.) of the main fraction was set aside for saponification. The remainder of the main fraction was redistilled and yielded a pale yellow oil, b.p. 122°/2 mm. (176 g.).

Anal. Calcd. for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.00; H, 8.21.

The distillation residue was combined with the fore-fraction and the dark oil previously obtained. The combined fractions were distilled and afforded additional material, b.p. 122°/2 mm., which raised the total yield to 70%.

Methyl 4-oxo-2-octenoate by pyrolysis of methyl bicyclo-[2.2.1]5-heptene-3-n-valeryl-2-carboxylate (V). The adduct (21.0 g., 0.089 mole) was pyrolyzed by subjecting it to two distillations under about 50-mm. pressure at a stillpot temperature of 180°. Vacuum fractionation of the pyrolysate yielded an oil, b.p. 104–109°/9 mm., which crystallized. The material was recrystallized from low boiling petroleum ether, m.p. 35–36°.

Anal. Calcd. for $C_9H_{14}O_3$: C, 63.51; H, 8.22. Found: C, 63.49; H, 7.94.

Pyrolysis of the distillation residue afforded additional material, b.p. 107–109°/9 mm. (2.0 g.; total yield, 11.4 g., 76%).

At somewhat higher pressures (80–100 mm.) pyrolysis of the lower molecular weight adducts tended to be complete in one to two passes. Also, distilled higher molecular weight "adducts" appeared to pyrolyze more readily, perhaps because of their initial admixture of material identical with the pyrolysis product.

Bicyclo[2.2.1]5-heptene-3-n-valeryl-2-carboxylic acid.[13] The portion of the once-distilled methyl ester that was set aside for saponification (10.6 g., 0.045 mole), potassium hydroxide (1.25 g., 0.022 mole), potassium carbonate (5.0 g., 0.036 mole), water (70 ml.), and methanol (85 ml.) were mixed and heated under reflux for 15 min. A portion of the solvent (65 ml.) was distilled off and heating under reflux continued for 4.5 hr. The solution was allowed to cool and stand at room temperature overnight. Addition of water to the cooled solution did not produce cloudiness. The solution was acidified by the addition of 3*N* hydrochloric acid. The resulting crystalline precipitate was filtered with suction and washed thoroughly with water and low boiling petroleum ether. After air-drying, the product had a melting point of 87–88° (8.1 g., 81% yield). On recrystallization from ligroin (b.p. 66–75°) the melting point was unchanged.

Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.12; H, 7.98.

Crude keto ester adducts (V) also can be saponified satisfactorily. In some cases higher over-all yields, on the basis of ester chlorides (IV), of keto acid adducts were obtained when the crude rather than the purified ester adducts (V) were subjected to saponification.

9,10-Dihydro-9,10-ethanoanthracene-12-carbomethoxy-11-carboxylic acid. A sodium methylate solution was prepared by reacting sodium (2.45 g., 0.1 atom) with methanol (100 ml.). The warm solution was stirred and 9,10-dihydro-9,10-ethanoanthracene-11,12-dicarboxylic anhydride (III) (27.6 g., 0.1 mole) was added to it in several portions. When the anhydride had dissolved, methanol was removed *in vacuo*. The residual syrup was taken up in water (100 ml.) and acidified with 3*N* hydrochloric acid. A curdy precipitate was obtained which gradually crystallized on being stirred with water. The crystallized material was filtered with suction and washed with water. Recrystallization from benzene yielded the methyl half ester, m.p. 209–210° (27.6 g., 90% yield).

Anal. Calcd. for $C_{19}H_{16}O_4$: C, 74.01; H, 5.23; neut. equiv. 308. Found: C, 74.40; H, 5.32; neut. equiv. 305.

9,10-Dihydro-9,10-ethanoanthracene-12-carbomethoxy-11-carbonylchloride (IV). A mixture of the half ester (111 g., 0.364 mole), thionyl chloride (55 g., 0.463 mole) and methylene chloride (200 ml.) was heated under reflux for 12 hr. following which the reaction mixture was concentrated *in vacuo* (water bath). The residue was dissolved in benzene (50 ml.) and the resulting solution again concentrated *in vacuo*. This procedure was repeated once more. The resulting crude ester chloride was dissolved in benzene for use in the following reaction. The benzene solution weighed 220 g., neut. equiv. 351.

*Methyl 9,10-dihydro-9,10-ethanoanthracene-12-n-valeryl-11-*carboxylate (V). *n*-Butylzinc chloride was prepared as described from 1.90*N* *n*-butylmagnesium bromide (242 ml.)

(12) R. G. Jones, *J. Am. Chem. Soc.*, **69**, 2350 (1947).

(13) For additional keto acid adducts and derived semicarbazones see Table I, following paper in this series, *J. Org. Chem.*, 22, 313 (1957).

and zinc chloride (63.5 g.) in ether (about 50 ml.). The above ester chloride solution in benzene was added and the resulting mixture was stirred overnight at 45°. After cooling, it was decomposed by the addition with stirring of dilute (1:3) hydrochloric acid and filtered. The clear benzene solution was separated, washed with water, and concentrated on the steam bath. The resulting residue was dissolved in warm isopropyl ether; the ensuing crystallization was slow. When it appeared complete, the crystalline material was filtered off and recrystallized from the same solvent, m.p. 104° (27 g., 21% yield on the basis of the half ester used).

Anal. Calcd. for $C_{23}H_{24}O_5$: C, 79.28; H, 6.94. Found: C, 79.22; H, 6.91.

Saponification with alcoholic alkali afforded a quantitative yield of the keto acid, m.p. 220–225°.

Anal. Calcd. for $C_{22}H_{22}O_5$: C, 79.01; H, 6.63; neut. equiv. 334. Found: C, 78.93; H, 6.58; neut. equiv. 336.

Methyl 4-oxo-2-octenoate by pyrolysis of methyl 9,10-dihydro-9,10-ethanoanthracene-12-n-valeryl-11-carboxylate (V). The adduct (7.0 g., 0.02 mole) was pyrolyzed at 260° under about 15-mm. pressure. The resulting distillate consisted of a solid (anthracene) and a yellow oil. The distillate was taken up in low boiling petroleum ether; the solution was filtered and partly concentrated. The concentrate deposited impure methyl 4-oxo-2-octenoate (m.p. 26°, 2.0 g., 59% crude yield). Recrystallization from the same solvent raised the melting point to 35°. No depression of the melting point resulted from admixture of the ester with a specimen of the ester obtained *via* the cyclopentadiene adduct (V).

Methyl 4-oxo-2-nonenoate from 4-oxo-2-nonenoic acid. 4-Oxo-2-nonenoic acid[7] (5.2 g., 0.031 mole) was dissolved in the calculated amount of 1*N* sodium hydroxide, and an excess of 40% silver nitrate solution was added. The precipitated silver salt was filtered off, washed with water and methanol, and dried at 40° *in vacuo* (6.8 g., 80% yield). A mixture of the silver salt, methanol (15 ml.), and methyl iodide (4.5 g., 0.032 mole) was heated under reflux for 2 hr. The solid material was removed by filtration and washed with a little methanol. The combined methanolic solutions were concentrated *in vacuo*. The residue was extracted with low boiling petroleum ether and the extract partly evaporated and allowed to crystallize. After two recrystallizations from low boiling petroleum ether, the ester melted at 45–46°.

Anal. Calcd. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.76. Found: C, 65.92; H, 8.54.

No depression of the melting point resulted upon admixture with a specimen of the ester, m.p. 48.5°, obtained *via* the cyclopentadiene adduct.

Acknowledgment. The author is indebted to Mr. S. J. Tassinari of this Laboratory who carried out the microanalyses, and to Dr. A. M. Vogel of the Chemistry Department, Adelphi College, Garden City, N. Y. for the ultraviolet absorption measurements.

OAKDALE, N. Y.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES DIVISION, NATIONAL DAIRY PRODUCTS CORPORATION]

Potential Antimicrobial Agents. II. 4-Hydroxy-2,4-alkadienoic Acid γ-Lactones[1]

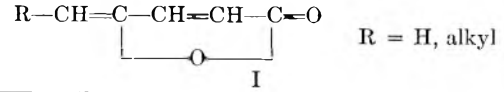
HENRY M. WALTON

Received September 17, 1956

A new method is described for the synthesis of 4-hydroxy-2,4-alkadienoic acid γ-lactones (protoanemonin analogs) in two steps: (1) Synthesis of cyclopentadiene and anthracene adducts of 4-oxo-2-alkenoic acids, followed by (2), lactonization and retrogressive Diels-Alder reaction of the resulting lactones. The facile saponification of the lactones also completes a new synthesis of 4-oxo-2-alkenoic acids.

Protoanemonin[2–4] and patulin,[5] both broad-spectrum antibiotics, are 4-hydroxy-2,4-alkadienoic acid γ-lactones, protoanemonin (I, R = H) being the simplest possible compound of this structure.

Since therapeutic use of these antibiotics appears to be precluded by their toxicity it seemed of interest to examine similar compounds in order to determine the relation of their structure to antimicrobial activity and toxicity.



I

When this investigation was undertaken protoanemonin was the only lactone of type I which had been synthesized. The most practicable synthesis of protoanemonin had been devised by Shaw[4] who obtained the lactone in 30% yield by lactonization of the readily available β-acetylacrylic acid. Although the lactonization of other 4-oxo-2-alkenoic acids might prove feasible, attempts in this direction appeared unpromising since these acids remain relatively inaccessible.[6,7]

(1) Preceding paper in this series: H. M. Walton, *J. Org. Chem.*, **22**, 308 (1957).

(2) For references concerning the physiological properties of this antibiotic see L. J. Haynes, *Quart. Rev.*, **2**, 46 (1948).

(3) Earlier findings concerning the physiological properties of this antibiotic were substantially confirmed by K. Rotter and Gruber, *Mitt. Versuchsanstalt Gärungsgewerbe u. Insts. angew. Mikrobiol. Hochschule Bodenkult.*, **3**, 56 (1949); [*Chem. Abstr.*, **47**, 7094 (1953)].

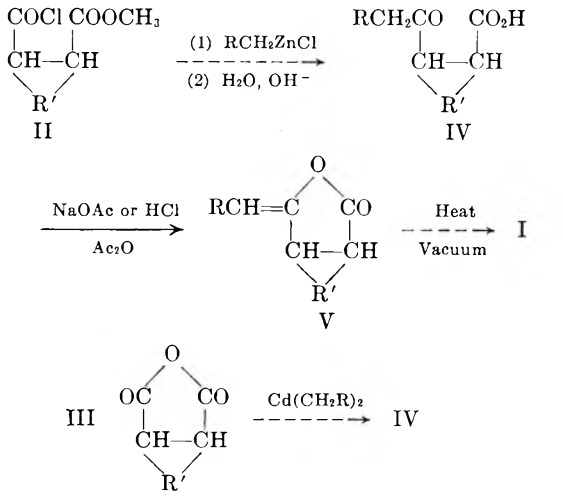
(4) Structure, *cf.* E. Shaw, *J. Am. Chem. Soc.*, **68**, 2510 (1946).

(5) R. B. Woodward and G. Singh, *J. Am. Chem. Soc.*, **71**, 758 (1949).

(6) For references concerning general methods of preparation for 4-oxo-2-alkenoic acids see (1).

(7) While this work was in progress, K. N. Campbell, C. D. Gordon and B. K. Campbell, Abstracts of Papers, 122nd Meeting, Am. Chem. Soc., Atlantic City 1952, p. 12L, outlined the synthesis of two lactones (I), R = *n*-propyl and R = *n*-amyl, by another route involving, *i. a.*, lactonization of 4-oxo-alkanoic acids, bromination of the resulting ketenol lactones and dehydrobromination.

A new method was, therefore, developed for the synthesis of lactones (I) which is based on Diels-Alder adducts of 4-oxo-2-alkenoic acids with cyclopentadiene and anthracene (IV). These adducts had become conveniently available through saponification of the corresponding esters obtained during an earlier investigation.[1] Lower molecular weight keto acid adducts (IV) proved also capable of preparation through the reaction of bicyclo-[2.2.1]5-heptene-2,3-dicarboxylic anhydride (III) with cadmium alkyls.



(II, IV: R′ = 3,5-cyclopenteno or 9,10-anthraceno; III: R′ = 3,5-cyclopenteno)

The corresponding lactones (V) represent adducts of 4-hydroxy-2,4-alkadienoic acid γ-lactones and it was reasonable to expect these lactone adducts to undergo retrogression[8] at elevated temperatures with the liberation of the desired lactones (I). This reaction scheme proved feasible.

could also be brought about by employing mixtures that resulted from the addition of small amounts of hydrochloric acid to acetic anhydride. However, this method appears to be limited to lower molecular weight members of the series (up to, and including, R = *n*-propyl). Attempts to apply acidic lactonizing conditions to higher homologs failed also when stronger, anhydrous acids (sulfuric, perchloric) in acetic anhydride were used.

The lactonization methods were successful when applied to keto acid adducts (IV) possessing an α-methylene group. Branching in the α-position apparently interferes with lactonization since attempts to lactonize the simplest α-branched keto acid adduct (IV) ($(CH_3)_2CH$— instead of RCH_2—) were unsuccessful.

Lactone adducts (V) were obtained as colorless high-boiling oils of considerable heat instability. Except in the case of the lowest molecular weight members of the series, they distilled with decomposition, *i.e.*, presumably retrogression,[8] even under low pressures (1 mm.).

The lactone adducts (V) with cyclopentadiene and anthracene underwent retrogression in a preparatively satisfactory manner at 180–200° and 240–260°, respectively. Higher over-all yields of lactones (I) were obtained when *crude* rather than purified lactone adducts (V) were subjected to pyrolysis.

The following yields of lactones (I) were obtained: From lactone adducts (V), 70–85%; from keto acid adducts (IV) without isolation of the intermediate lactone adducts (V), 50–80%; on the basis of half ester chlorides (II) yields were generally 25–40%.

The alkadienoic lactones (I) were obtained as

TABLE I

KETO ACID ADDUCTS (IV)

R	M.P. °C.	Formula	Analyses[a] C Calcd.	C Found	H Calcd.	H Found
CH_3	102–103[b]	$C_{11}H_{14}O_3$	68.03	67.41	7.27	7.04
C_2H_5	83–85[c]	$C_{12}H_{16}O_3$	69.20	69.36	7.75	7.94
[d]	85–86[c]	$C_{12}H_{16}O_3$	69.20	69.07	7.75	7.43
n-C_3H_7	87–88[c,e]	$C_{13}H_{18}O_3$	70.24	70.12	8.16	7.98
i-C_3H_7	122[b]	$C_{13}H_{18}O_3$	70.24	70.07	8.16	8.10
n-C_4H_9	93–94[f]	$C_{14}H_{20}O_3$	71.16	71.50	8.53	8.48
n-C_5H_{11}	85[c,g]	$C_{15}H_{22}O_3$	71.97	72.23	8.86	8.54
n-$C_{11}H_{23}$	86.5–87[c,h]	$C_{21}H_{34}O_3$	75.40	74.94	10.27	9.99

[a] Neutral equivalents found 100–101% of theory. [b] Recrystallized from isopropyl ether. [c] Recrystallized from ligroin, b.p. 60–90°. [d] $(CH_3)_2CH$ instead of RCH_2. [e] Semicarbazone from aqueous dioxane, m.p. 209–211°, dec. Calcd. for $C_{14}H_{23}N_3O_3$: C, 56.25; H, 7.80. Found: C, 56.27 H, 7.47. [f] Recrystallized from isopropyl ether-ligroin. [g] Semicarbazone from aqueous alcohol, m.p. 183–184.5°. Calcd. for $C_{16}H_{25}N_3O_3$: C, 62.51; H, 8.20. Found: C, 62.52; H, 7.98. [h] Semicarbazone from aqueous alcohol, m.p. 130–131°. Calcd. for $C_{22}H_{37}N_3O_3$: C, 67.49; H, 9.52. Found: C, 67.70; H, 9.25.

Generally, the keto acid adducts (IV) were lactonized in refluxing acetic anhydride containing small amounts of sodium acetate. Lactonization

(8) For a discussion of the retrogressive Diels-Alder reaction see M. C. Kloetzel, *Org. Reactions*, **4**, 9 (1948).

colorless oils of pleasant, characteristic odor. They lack the lachrymatory and vesicant properties of their parent compound, protoanemonin. The new lactones (I), on storage under nitrogen at room temperature, showed only a moderate discoloration,

TABLE II

LACTONES (I)

R	B.P. °C.	Mm.	Formula	Analyses[a] C Calcd.	C Found	H Calcd.	H Found	n_D^{25}
CH_3[b]	94–95	10	$C_6H_6O_2$	65.44	65.58	5.49	5.56	1.5316
n-C_3H_7[c]	65–67	1	$C_8H_{10}O_2$	69.54	69.51	7.30	7.16	1.5182
	118–120	17						
i-C_3H_7	110–113	11	$C_8H_{10}O_2$	69.54	69.35	7.30	7.07	1.5085
n-C_4H_9	131–132	18	$C_9H_{12}O_2$	71.02	70.20	7.94	7.72	
n-C_5H_{11}	154–156	18	$C_{10}H_{14}O_2$	72.26	72.45	8.49	7.87	1.5088

[a] Saponification equivalents found were 100–103% of theory. [b] Cyclopentadiene adduct: b.p. 119–124°/0.8 mm. Calcd. for $C_{11}H_{12}O_2$: C, 74.98; H, 6.87. Found: C, 74.46; H, 6.73. [c] Anthracene adduct: m.p. 176° (from methyl ethyl ketone). Calcd. for $C_{22}H_{20}O_2$: C, 83.52; H, 6.37. Found: C, 83.67; H, 6.35.

apparently without occurrence of appreciable dimerization.

The alkadienoic lactones (I) underwent the usual tests for unsaturation and gave a positive Legal test. Their ultraviolet absorption was consistent with values reported for patulin,[4] λ_{max} 276 mμ and desoxypatulin,[4] λ_{max} 273 mμ. 4-Hydroxy-2,4-nonadienoic acid γ-lactone had $\lambda_{max}^{isopropyl\ alcohol}$ 275 mμ, ε 17,700; 4-hydroxy-2,4-decadienoic acid γ-lactone had $\lambda_{max}^{isopropyl\ alcohol}$ 280 mμ, ε 15,700.

Lactones (I) were easily saponified. Saponification followed by acidification afforded known 4-oxo-2-alkenoic acids,[7] thus confirming the carbon skeletal structures of lactones (I) as obtained by the present method. Yields of 60–70% of 4-oxo-2-alkenoic acids were realized from lactones (I).

4-Oxo-2-alkenoic acids were also obtained in small yields by direct pyrolysis of keto acid adducts (IV).

EXPERIMENTAL

Melting points were determined on a Fisher-Johns melting point apparatus; the thermometer was calibrated with Keufler "Testsubstanzen." Boiling points are uncorrected.

Bicyclo[2.2.1]5-heptene-3-propionyl-2-carboxylic acid (IV). (*R* = *ethyl*, *R″* = *3,5-cyclopenteno-*) *from II and diethyl cadmium.* The preparation of the Grignard reagent, its reaction with cadmium chloride and the subsequent condensation with II were conducted under dry nitrogen. An efficient stainless steel stirrer and a Teflon bearing were used.

Ethylmagnesium bromide was prepared in the usual way from magnesium (24.3 g., 1 atom) and ethyl bromide (122 g., 1.14 moles) in ether (500 ml.). Cadmium chloride (96 g., 0.525 mole) was added in several portions to the Grignard solution (ice bath). The mixture was then stirred briefly at room temperature. Stirring was maintained throughout the following operations. The mixture was heated for 30 min. under reflux. A solution of II (109.5 g., 0.67 mole) in benzene (700 ml.) was added rapidly. The reaction temperature was raised to about 80° by distilling off ether and replacing it with benzene; three fractions of distillate were collected, namely, up to 62°, 62–74°, and 74–77°; at 62°, 74°, and at 77°, the original volume of the distilling mixture was restored by the addition of benzene (a total of 850 ml.). Following this, the mixture was heated under reflux for 4 hr., cooled, and decomposed by the slow addition, with external cooling, of 3*N* hydrochloric acid (300 ml.). The separated aqueous layer was extracted with benzene. The combined benzene solutions were washed with water and extracted with 10% potassium carbonate solution (750 ml.). The separated basic extract was acidified with 3*N* hydrochloric acid. The resulting mixture was stirred briefly. The precipitated crude product was filtered, washed with water, and air-dried. Recrystallization from acetone afforded colorless crystals, m.p. 101.5–103.5° (yield 34 g.). A second crop, m.p. 101.5–102° (17 g., total yield 35%), was obtained from the recrystallization mother liquors.

Lactones (V). (*R″* = *3,5-cyclopenteno-*). The lactones were isolated from their crude concentrates by distillation under 1 mm. pressure. Their preparation and, when desired, their pyrolysis followed the procedures described below.

Lactones (V). (*R″* = *9,10-anthraceno-*). A mixture of keto acid adduct (IV, R = *n*-propyl[1]; (14 g., 0.042 mole), acetic anhydride (56 g., distilled from sodium acetate) and sodium acetate (0.40 g., 0.005 mole) was heated for 17 hr. under reflux in a nitrogen atmosphere. The solvent was distilled *in vacuo* (water bath). A buff-colored solid was left which was digested with a small amount of methyl ethyl ketone and filtered. Digestion and filtration were repeated once. The lactone (VI), m.p. 176° (8.0 g., 60% yield) crystallized from the combined filtrates at room temperature.

Anal. Calcd. for $C_{22}H_{20}O_2$: C, 83.52; H, 6.37. Found: C, 83.67; H, 6.35.

After prolonged standing at 5°, the mother liquors deposited additional lactone (4.5 g.) which raised the total yield to 93%.

Lactones (I) *from keto acid adducts* (IV). (*A*) *From cyclopentadiene adducts* (*R″* = *3,5-cyclopenteno-*), *use of hydrochloric acid–acetic anhydride mixture.* Bicyclo[2.2.1]5-heptene-3-propionyl-2-carboxylic acid (IV, R = ethyl; 17.5 g., 0.09 mole) was added to a mixture of acetic anhydride (35 g.) and concentrated hydrochloric acid (1.8 g.) and stirred until solution had occurred (30 min.). The solution was allowed to stand at room temperature for several hours. It was filtered to remove traces of solid, and concentrated *in vacuo*. The residue was pyrolytically distilled under about 70 mm. pressure, and the distillation completed under 15 mm. pressure. Redistillation of the pyrolysate yielded the lactone as a colorless oil, b.p. 91–96°/12 mm. (7.25 g., yield 63%).

Anal. Calcd. for $C_6H_6O_2$: C, 65.44; H, 5.49; 2 double bonds. Found: C, 65.58; H, 5.56; hydrogen uptake, 2.0 moles.

(*B*) *From cyclopentadiene adducts* (*R″* = *3,5-cyclopenteno-*), *use of sodium acetate in acetic anhydride.* A mixture of bicyclo[2.2.1]5-heptene-3-*n*-valeryl-2-carboxylic acid (IV, R = *n*-butyl; 55.5 g., 0.25 mole), sodium acetate (1.1 g., 0.013 mole) and acetic anhydride (278 g., distilled from sodium acetate) was heated under reflux for 5 hr. in a nitrogen atmosphere. The solvent was distilled off *in vacuo* through a short Vigreux column and redistilled in the same

manner. The distillation residues were combined and taken up in ether. Undissolved solid material was removed by filtration and washed with ether. The combined ethereal solutions were concentrated *in vacuo*. The concentrate was pyrolyzed under 110 mm. pressure and the distillation terminated under 20 mm. pressure. Most of the pyrolysate was obtained at 165–170°/110 mm. Toward the end of this and similar pyrolysis runs, small amounts of solid material were obtained which were identified as 4-oxo-2-alkenoic acids, corresponding to keto acid adducts (IV). Distillation of the pyrolysate gave a fraction, b.p. 123–127°/17 mm., which upon redistillation yielded the lactone as a colorless oil, b.p. 110–111°/10 mm. (20.15 g., yield 59%); sapon. equiv. calcd. and found: 138.

In a repeat run in which the stripped and redistilled solvent was used, a 68% yield, b.p. 119–121°/15 mm., was obtained.

(*C*) *From anthracene adducts* (*R″ = 9,10-anthraceno-*). Lactone (VI), (8.0 g., 0.025 mole) was pyrolyzed at 240–260° under 12 mm. pressure. The distillate consisted of copious amounts of anthracene and a yellow oil. Low boiling petroleum ether was added to the mixture, and the solution was filtered and concentrated. Distillation yielded a colorless oil, b.p. 110–112°/11 mm. (1.9 g., yield 54%); sapon. equiv. calcd., 138; found, 142.

2,4-Octadienoic acid by saponification of 4-hydroxy 2,4-octadienoic acid γ-lactone. The lactone (1.35 g., 0.0098 mole) was dissolved in a little acetone, and treated with 1*N* sodium hydroxide (10 ml.). Enough acetone was added to the mixture to make it homogeneous. After standing at room temperature for 15 min. the solution was neutralized to the phenolphthalein end point with 0.1*N* hydrochloric acid, extracted twice with small amounts of methylene chloride, acidified with 3*N* hydrochloric acid and extracted with ether. The ethereal solution was separated, washed with water, and allowed to evaporate at room temperature. The residue was taken up in a small amount of isopropyl ether containing a trace of iodine. Crystallization began within a few hours; when it appeared complete, the mass was filtered, washed with a mixture of isopropyl ether and low boiling petroleum ether and finally with petroleum ether. Air-drying resulted in a 64% yield (0.98 g.) of colorless needles, m.p. 108° (reported[9] m.p. 105–106°); neut. equiv. calcd. and found: 156.

Acknowledgment. The author is indebted to Mr. S. J. Tassinari for the reported microanalyses, and to Mr. Berruti for ultraviolet absorption data.

OAKDALE, N. Y.

(9) F. L. Breusch and H. Keskin, *Arch. Biochem.*, **18**, 314 (1948).

[CONTRIBUTION FROM THE RESEARCH LABORATORIES DIVISION, NATIONAL DAIRY PRODUCTS CORPORATION]

Potential Antimicrobial Agents. III. 4-Methylamino-2,4-alkadienoic Acid γ-Lactams[1]

HENRY M. WALTON

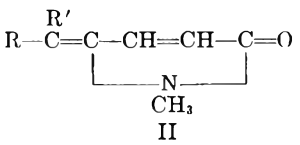
Received September 17, 1956

4-Methylamino-2,4-alkadienoic acid γ-lactams are structurally analogous to the antibiotic, protoanemonin. For this new class of lactams, a convenient one-step method of preparation is presented, consisting of the reaction of Grignard reagents with N-methylbicyclo[2.2.1]5-heptene-2,3-dicarboximide, followed by pyrolysis of the resulting Diels-Alder lactam adducts.

The structures of protoanemonin[2] and patulin[3] have attracted attention to 4-hydroxy-2,4-alkadienoic acid γ-lactones (I) as potential antimicrobial agents.[4] The preceding paper in this series[1] describes a general method for the preparation of lactones (I). It seemed also of interest to determine what effect the replacement of the lactone ring oxygen by nitrogen might have on physiological action.

This paper is concerned with the preparation of a new class of lactams (II) structurally analogous to lactones (I), in which the N-methyl group takes the place of the lactone ring oxygen.

The method presented here is based on the use of

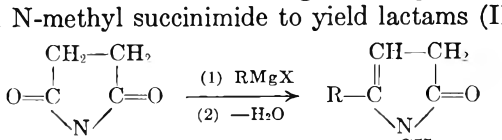


II

R, R′ = H, alkyl, cycloalkyl

the Diels-Alder adduct of N-methyl maleimide and cyclopentadiene, N-methylbicyclo[2.2.1]5-heptene-2,3-dicarboximide (IV), which is easily accessible, through reaction of the commercially available bicyclo[2.2.1]5-heptene-2,3-dicarboxylic anhydride[5] with methylamine.

Lukes[6] has shown that Grignard reagents react with N-methyl succinimide to yield lactams (III):



III

(1) Preceding paper in this series: H. M. Walton, *J. Org. Chem.*, **22**, 312 (1957).

(2) E. Shaw, *J. Am. Chem. Soc.*, **68**, 2510 (1946).

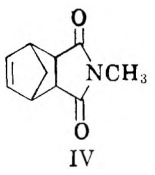
(3) R. B. Woodward and G. Singh, *J. Am. Chem. Soc.*, **71**, 758 (1949).

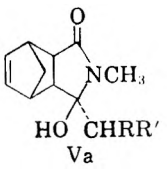
(4) For a discussion of the antimicrobial activity of unsaturated lactones, see L. J. Haynes, *Quart. Rev.*, **2**, 46 (1948); C. J. Cavallito, Antibiotics from Plants, in C. M. Suter, *Medicinal Chemistry*, John Wiley and Sons, New York, 1951, Vol. I, pp. 224–235.

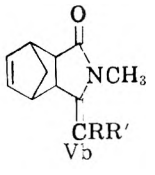
(5) Nadic Anhydride, National Aniline Division, Allied Chemical and Dye Corporation.

(6) R. Lukes, *Coll. Czechoslov. Chem. Comm.*, **1**, 119 (1929); *Chem. Abstr.*, **23**, 4469 (1929).

Similarly the reaction of Grignard reagents with imide adduct (IV) yielded lactams (Vb), with or without isolation of their hydrated precursors (Va.)


IV


Va


Vb

A number of Diels-Alder adducts similar to (IV) are known to be thermally unstable and to undergo retrogression[7] at elevated temperatures with the liberation of the corresponding maleimides.[8] It was found that the new adducts (Vb) easily undergo pyrolytic retrogression at 180–200°.

The amide adduct (IV) reacted readily with Grignard reagents derived from primary, secondary, cycloalkyl, and benzyl halides. In the reaction of Grignard reagents of primary alkyl halides, adducts (Vb) were obtained in 65–90% yield. Efficient stirring was essential for optimal yield. After working up the reaction mixture, adducts (Va, Vb) or lactams (II) were obtained depending upon conditions encountered during isolation.

In a number of cases, when low temperatures could be maintained during isolation, adducts (Va) resulted. Their separate dehydration and conversion into adducts (Vb) was easily effected by refluxing their benzene solutions containing small amounts of p-toluenesulfonic acid, and azeotropic water removal.

When moderate temperatures were encountered during isolation, the dehydrated product (Vb) resulted directly, *e.g.*, when following hydrolysis the benzene solution of the crude reaction product was concentrated on the steam bath. Also, in a few cases involving lower molecular weight adducts (Vb), the distilled product contained unreacted imide adduct (IV) which could not be completely removed although it tended to partly crystallize from the distillate.

Attempted distillations of the Grignard reaction product at still pot temperatures of 175° and higher resulted in varying degrees of retrogression with the formation of lactams (II).

Table I lists a series of intermediate lactam adducts (Va, Vb).

TABLE I

LACTAM ADDUCTS (Va, Vb)

R	R′	M.P. or B.P. °C./Mm.	Formula[a,b]	Analyses C Calcd.	C Found	H Calcd.	H Found
n-C_3H_7	H	123.5–125.5°/1.5	$C_{14}H_{19}NO^{b,c}$	77.38	76.56	8.81	8.62
n-C_3H_7	H	126–127°[d]	$C_{14}H_{21}NO_2^{a,e}$	71.42	71.87	8.99	8.91
n-C_5H_{11}	H	117–119.5°/0.2	$C_{16}H_{23}NO^{b}$	78.32	78.10	9.45	9.38
n-C_7H_{15}	H	158–161°/0.3	$C_{18}H_{27}NO^{b}$	79.06	78.74	9.96	9.83
n-$C_{11}H_{23}$	H	65–66[f]	$C_{22}H_{37}NO_2^{a}$	76.03	76.00	10.73	10.58
CH_3	CH_3	149–150°[d]	$C_{13}H_{19}NO^{b}$	70.65	70.89	8.65	8.41
C_6H_5	H	170–175° dec.[g]	$C_{17}H_{19}NO_2^{a}$	75.81	75.92	7.11	7.10
—$(CH_2)_5$—		168–169°[d]	$C_{16}H_{23}NO_2^{a}$	73.53	73.41	8.87	8.70

[a] Structure (Va). [b] Structure (Vb). [c] Analysis suggests the admixture of (Va) or of (IV). [d] Recrystallized from methyl ethyl ketone. [e] Analysis suggests the presence of (Vb). [f] Recrystallized from isopropyl ether, then from ether-petroleum ether mixture. [g] Recrystallized from isopropyl alcohol.

The lactam adducts appear to be somewhat more heat-stable than the corresponding adducts of lactones (I). The *crude* lactams may be pyrolyzed directly. The new method essentially consists of one step affording lactams (II) in 50–85% overall yields.

Lactams (II) and lactam adducts (Vb) were usually obtained as colorless to pale yellow oils, which, in the absence of precautions, tended to thicken and discolor upon storage. However, little deterioration was observed when these materials were stored under nitrogen at about 4°. Solid adducts (Va) were stored at room temperature for two years without apparent change.

The skeletal structure of lactams (II) was confirmed by conversion of 4-methylamino-2,4-octadienoic acid γ-lactam (VI) and 4-methylamino-3-octenoic acid γ-lactam (VII) to sodium 4-methylamino octanoate (VIII) *via* parallel reaction series, and characterization of the corresponding acids as N-3,5-dinitrobenzoyl derivatives. The 3,5-dinitrobenzamides so obtained had m.p. 57–58°, separate and admixed.

Lactam (VI) in isopropyl alcohol had λ_{max} 262 mμ, ε 9924, with a secondary peak at 300 mμ. This compares with the following absorption maxima of lactones of related structure: protoanemonin,[2] λ_{max} 260 mμ; patulin,[3] λ_{max} 276 mμ; 4-hydroxy-2,4-nonadienoic acid γ-lactone,[1] λ_{max} 275 mμ.

(7) For a discussion of the retrogressive Diels-Alder reaction see M. C. Kloetzel, *Org. Reactions*, IV, 9 (1948).

(8) E. J. Prill, U. S. Patent 2,524,136; *Chem. Abstr.*, 45, 1162 (1951); P. O. Tawney, U. S. Patent 2,524,145; *Chem. Abstr.*, 45, 1162 (1951); *cf.* St. C. Harvey, *J. Am. Chem. Soc.*, 71, 1121 (1949); J. A. Berson and R. Swidler, *J. Am. Chem. Soc.*, 76, 2835 (1954).

TABLE II

LACTAMS (II)

R	R′	M.P. or B.P. °C./Mm.	Formula	Analyses C Calcd.	C Found	H Calcd.	H Found
C_2H_5	H	122–124°/15	$C_8H_{11}NO$	70.04	70.14	8.08	7.81
n-C_3H_7	H	132–133°/11	$C_9H_{13}NO$	71.49	71.84	8.66	8.34
n-C_5H_{11}	H	154°/10	$C_{11}H_{17}NO$	73.38	73.34	9.56	9.54
n-C_7H_{15}	H	177–179°/12	$C_{13}H_{21}NO$	75.31	74.28	10.21	9.84
CH_3	CH_3	98–99°[a]	$C_9H_{11}NO$	70.04	70.02	8.08	8.01
CH_3	n-C_6H_{13}	190°/17	$C_{13}H_{21}NO$	75.31	75.04	10.21	10.03
—$(CH_2)_5$—		117–118°[b]	$C_{11}H_{15}NO$	74.54	74.83	8.53	8.36

[a] Recrystallized from isopropyl ether. [b] Recrystallized from isopropyl ether-methyl ethyl ketone.

In view of their ready accessibility, attempts were made to convert lactams II into methyl 4-oxo-2-alkenoates, as an alternative to the method described earlier for the preparation of these esters.[9] Numerous attempts failed to bring about a satisfactory conversion by means of methanol and acids.

EXPERIMENTAL

All melting points were determined on a Fisher-Johns melting point apparatus, thermometer calibration with Keufler "Testsubstanzen."

N-Methylbicyclo[2.2.1]5-heptene-2,3-dicarboximide (IV). With intermittent stirring, 40% methylamine (120 g., 1.55 mole) was added in several portions to bicyclo[2.2.1]5-heptene-2,3-dicarboxylic anhydride (164 g., 1.0 mole). The resulting reaction was moderated by cooling the mixture in a water bath. During the addition of the amine the anhydride went into solution. Shortly afterwards the flask contents solidified. They were heated in an oil bath at 160–180° until the distillation of water ceased (about 30 min.). The crystalline mass obtained on cooling was taken up in hot isopropyl alcohol. When the solution was filtered and cooled it deposited the product (148 g., 85% yield) of colorless crystals, m.p. 107°; reported m.p. 105–107°.[10]

Lactam (Va) (RR' = —$(CH_2)_5$—). The preparation of all Grignard reagents and their reaction with imide (IV) were carried out under dry nitrogen. An efficient stainless steel stirrer was used to maintain stirring throughout. Cyclohexylmagnesium bromide was prepared in the usual manner from magnesium (4.0 g., 0.165 g. atom) and cyclohexyl bromide (freshly distilled, 28.0 g., 0.172 mole) in ether (100 ml.). The reaction was initiated with the aid of a small amount of methylmagnesium iodide solution and completed with stirring and heating under reflux for several hours. The imide (IV) (26.6 g., 0.15 mole) dissolved in benzene (130 ml.) was added with stirring to the Grignard solution at a rate sufficient to maintain spontaneous refluxing. The precipitate formed during addition of the imide solution became very viscous, and rendered stirring difficult, when the addition was about half completed. With continued stirring and addition of the imide solution, the viscous mass gradually became granular and the fluidity of the mixture was restored. Following the addition, stirring and heating under reflux were continued for 8.5 hr. The reaction mixture was allowed to cool and stand at room temperature overnight. It was decomposed by the cautious addition with external cooling of water (50 ml.), followed by 3N hydrochloric acid (55 ml.). The resulting crystalline precipitate was removed by filtration and washed with water and ether. The washed solid (30 g., m.p. 165–173°) was dissolved in hot methyl ethyl ketone and allowed to crystallize. Coarse needles, m.p. 168–169°, were obtained.

Anal. Calcd. for $C_{16}H_{23}O_2N$: C, 73.53; H, 8.87. Found: C, 73.41; H, 8.70.

Additional material was obtained by working up the filtrates.

Lactam (Vb) (R = n-C_5H_{11}, R' = H). The Grignard reagent was prepared from magnesium (7.3 g., 0.30 g. atom) and n-hexyl chloride (36.5 g., 0.33 mole) in ether (150 ml.) and reacted with imide (IV) (44.3 g., 0.25 mole) dissolved in benzene (220 ml.) as described above. After completion of the addition the mixture was stirred and heated under reflux for 1.5 hr. It was cooled and decomposed by the gradual addition, with stirring and external cooling, of 3N hydrochloric acid (100 ml.). The aqueous layer was separated and extracted with ether. The combined ethereal solutions were washed with several small portions of water, dried over magnesium sulfate and concentrated *in vacuo* (water bath to 80°). A light yellow oil (60.4 g.) was obtained. A portion of the oil (9.1 g.) was distilled and yielded a pale yellow oil, b.p. 117.5–119.5°/0.2 mm. (5.1 g., corresponding to a 76% yield).

Anal. Calcd. for $C_{16}H_{23}NO$: C, 78.32; H, 9.45. Found: C, 78.10; H, 9.38.

Lactam (II) (R = n-C_3H_7, R' = H). The corresponding adduct (Vb) (5.5 g., 0.025 mole) was heated to 190–200° under about 60 mm. pressure and the distillation was completed under 15 mm. pressure. Redistillation of the pyrolysate yielded a colorless oil (2.7 g., yield 71%), b.p. 132–133°/11 mm., n_D^{25} 1.5472, which was stored under nitrogen.

Anal. Calcd. for $C_9H_{13}NO$: C, 71.49; H, 8.66, 2 double bonds. Found: C, 71.84; H, 8.34. H_2 uptake, 2.0 mole.

Other adducts similarly were pyrolyzed.

4-Methylaminooctanoic acid γ-lactam from 4-methylamino-2,4-octadienoic acid γ-lactam (VI). The solution of the unsaturated lactam, b.p. 130°/10 mm. (16.0 g.) in alcohol (50 ml.) was hydrogenated at room temperature using an initial pressure of 27.5 lb. and a 10% palladium on charcoal catalyst. Hydrogen uptake was quantitative. Filtration and distillation resulted in the quantitative yield of a colorless oil, b.p. 120°/10 mm., n_D^{25} 1.4695.

Anal. Calcd. for $C_9H_{17}ON$: C, 69.63; H, 11.04. Found: C, 69.99; H, 10.48.

Despite the apparently quantitative hydrogen uptake, analyses and refractive index indicated the presence of incompletely hydrogenated lactam VI.

4-Methylaminooctanoic acid γ-lactam from 4-methylamino-3-octenoic acid γ-lactam (VII). By the foregoing procedure the unsaturated lactam,[3] b.p. 120–122°/8 mm., yielded a colorless oil, b.p. 121–124°/11 mm., n_D^{25} 1.4670.

Anal. Calcd. for $C_9H_{17}ON$: C, 69.63; H, 11.04. Found: C, 69.34; H, 10.89.

N-3,5-Dinitrobenzoyl-4-methylaminooctanoic acid. Both saturated lactams were treated as follows:

(9) Paper I in this series, H. M. Walton, *J. Org. Chem.*, **22**, 308 (1957).

(10) H. W. Arnold and N. E. Searle, U. S. Patent 2,462,-835; *Chem. Abstr.*, **43**, 4421 (1949).

The lactam (3.4 g.) was dissolved in 3*N* hydrochloric acid (8 ml.) and allowed to stand at room temperature for 40 hr. To the resulting mixture 3*N* sodium hydroxide (15 ml.) was added and the precipitated oil redissolved by the addition of water (total weight of solution: 40 g.).

A portion of this solution (10 ml.) was stirred with 3,5-dinitrobenzoyl chloride (2 g.). After a few minutes the mixture was filtered and acidified with hydrochloric acid. The resulting solid material was filtered off, washed with water and ether, and dissolved in a small amount of hot benzene. The benzene solution was concentrated on the steam bath and the residue crystallized from a mixture of isopropyl ether and ligroin. Recrystallization from the same solvent mixture yielded faintly yellow crystals, m.p. 57–58°, in both reaction series. The same melting point was observed with a mixture of the two specimens.

Anal. (specimen derived from lactam VI). Calcd. for $C_{15}H_{21}N_3O_7$: C, 52.03; H, 5.73. Found: C, 51.81; H, 5.31.

Acknowledgment. The author is indebted to Mr. S. J. Tassinari for microanalyses and to Mr. R. Berruti for ultraviolet absorption data.

OAKDALE, N. Y.

Notes

A department for short papers of immediate interest.

Unsaturated Fatty Acids. IV. Preparation of Oleic-1-C^{14} Acid[1]

JUDD C. NEVENZEL AND DAVID R. HOWTON

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By a series of reactions analogous to that employed earlier[2] in the preparation of linoleic-1-C^{14} acid, oleic-1-C^{14} acid has now been synthesized by radiocarbonation of the Grignard reagent of *cis*-1-bromo-8-heptadecene, which was obtained *via* *threo*-9,10-dibromooctadecanoic acid, its silver salt, and *threo*-1,8,9-tribromoheptadecane.

The acid was treated with diazomethane to give methyl oleate-1-C^{14}, which has been used in metabolism studies reported elsewhere.[3] This synthesis of oleic-1-C^{14} acid is to be compared with that reported recently by Bergström and coworkers,[4] which differs from that presently employed only in protection of the *cis*-double bond by hydroxylation (instead of bromination) and in introduction of the labeled carboxy carbon by a nitrile synthesis instead of by a Grignard carbonation. Although the Bergström synthesis involves four labeled-reactant steps, while isotope is introduced in the final step of the present method, the isotope yields realized are comparable—48[4] and 59%.

EXPERIMENTAL

Unless otherwise indicated, reactions were conducted as described in detail previously.[2] Ultimate analyses were performed by Dr. A. Elek (Elek Micro Analytical Laboratories, Los Angeles), infrared absorption analyses by Mr. Paul Kratz, and some of the radioactivity determinations by Mr. W. H. Slaton, Jr. All melting points are corrected. Reported *trans*-contents of olefinic substances, based on infrared absorption at 10.3μ, are considered to be within 5% of actual values.

Purified oleic acid was obtained[5] from commercial material (Merck U.S.P.) by fractional distillation, low-temperature crystallization (from 10% solution in acetone at -20 to $-50°$), and redistillation, b.p. 168–173° at about 200μ, water-white, m.p. 10°, n_D^{25} 1.4580; this material is expected to contain about 3% each of linoleic[6] and saturated acids,[5] all or part of which may persist as contaminants in the labeled oleic acid (see below).

threo-9,10-Dibromooctadecanoic acid (I). Although this substance has been employed in a great number of published investigations, in only one instance[7] has it been reported as a crystalline compound, m.p. 28.5–29°. Inasmuch as oleic acid is difficult to obtain in a high state of purity and since, moreover, addition of bromine to the acid is accompanied by some 8–10% of anomalous substitution reactions (giving rise to hydrogen bromide and bromine substituents in positions other than 9 and 10 of the stearic acid skeleton[8]), the reported crystallizability of I was of interest from the standpoint of suggesting an additional means of purification. By mixing equivalent amounts of oleic acid and bromine in carbon tetrachloride at 0°, a sample of I was obtained which crystallized spontaneously on standing neat for a short time at $-10°$. This material had a crude melting point of 20–24° and a refractive index (n_D^{42}) of 1.4878 (lit.[7] n_D^{42} 1.4878), and was shown by chromatography on alumina[9] of the methyl ester prepared from it with diazomethane to be essentially free of unbrominated and tetrabromide contaminants and by infrared absorption studies on the zinc-debrominated ester to be free of the *erythro*-9,10-dibromodiastereoisomer.[10] But despite the apparent purity of the preparation, low-temperature recrystallization failed to result in good recovery of material of improved purity (as judged by melting point; repeated crystallization starting with 8.4 g. of crude I gave 0.32 g. of solid, m.p. 27–28°)[13]; consequently the crude product obtained under conditions designed to minimize anomalous substitution was employed.

In a nitrogen atmosphere, a solution of 28.2 g. (0.1 mole) of purified oleic acid and 0.28 g. of di-*t*-butyl-*p*-cresol (Koppers Co.) in 200 ml. of carbon tetrachloride was heated to boiling (to drive traces of moisture from the reactants and apparatus), cooled to 0°, and treated dropwise with dry bromine (16 g., 0.1 mole) over a period of about 30 min.;

(1) This paper is based on work performed under Contract AT-04-1-GEN-12 between the Atomic Energy Commission and the University of California at Los Angeles.

(2) D. R. Howton, R. H. Davis, and J. C. Nevenzel, *J. Am. Chem. Soc.*, 76, 4970 (1954).

(3) J. F. Mead, W. H. Slaton, Jr., and A. B. Decker, *J. Biol. Chem.*, 218, 401 (1956).

(4) S. Bergström, K. Pääbo, and M. Rottenberg, *Acta Chem. Scand.*, 6, 1127 (1952); the authors are indebted to Prof. Bergström for making available a manuscript of this work prior to its publication.

(5) D. Swern, H. B. Knight, and T. W. Findley, *Oil & Soap*, 21, 133 (1944).

(6) Oleic acid having a lower linoleic acid content may be obtained from olive oil fatty acids by a similar procedure; cf. H. B. Knight, E. F. Jordan, Jr., E. T. Roe, and D. Swern, *Biochemical Preparations*, 2, 100 (1952).

(7) D. Holde and A. Gorgas, *Z. angew. Chem.*, 39, 1443 (1926).

(8) Unpublished observations.

(9) D. R. Howton, *Science*, 121, 704 (1955).

(10) The apparently good stereospecificity of the bromination-zinc-debromination cycle as applied to oleic acid is in agreement with findings (based on less sensitive methods) of Nicolet[11] and of Holde and Gorgas,[7] although at odds with results obtained on simpler olefins[12]; and is of interest in connection with the rather appreciable *trans*-content of the reconstituted oleic acid obtained in the present study (see below).

(11) B. H. Nicolet, *J. Am. Chem. Soc.*, 43, 2122 (1921).

(12) W. G. Young, S. J. Cristol, and T. Skei, *J. Am. Chem. Soc.*, 65, 2099 (1943).

(13) The low crystallizability of I compared with that of the structurally and physically closely similar *erythro*-isomer (m.p. 29.5–30.0°, prepared in the same way from elaidic acid) is strikingly illustrated by cooling 10% solutions of the two substances in n-pentane in 5°-increments; the *erythro*-acid crystallizes out in good yield at $-15°$, while the *threo*-acid does not emerge in appreciable amount until the solution is cooled to $-50°$.

decolorization was rapid until about 90% of the bromine had been added. After stirring an additional 30 min. at 0°, the still-colored mixture was shaken with aqueous sodium bisulfite (discharging the color), then with water until free of mineral acid, and dried over magnesium sulfate. Solvent was stripped from the crude product (44.5 g.), which was dissolved in 450 ml. of acetone and stirred at −20° for 75 min., precipitating a small amount of solid (presumably bromine-free and tetrabromo contaminants), which was removed by filtration. Removal of solvent from the filtrate left 43.3 g. (98%) of crude I, viscous brown oil, which was employed directly in preparation of the silver salt (II).

Methyl threo-9,10-dibromooctadecanoate was prepared from the recrystallized sample of I (m.p. 27–28°) by treatment with excess ethereal diazomethane. The ester gave a copious precipitate on warming with ethanolic silver nitrate, and a perceptible cloudiness after only 15 min. at room temperature. The reactivity of the bromine substituents in this material, reflected in the instability of the silver salt of I (see below), is to be compared with that of those in methyl *threo,threo*-9,10,12,13-tetrabromooctadecanoate, which does not react detectably with silver nitrate in 15 hr. at room temperature.[2]

Silver threo-9,10-dibromooctadecanoate (II) was prepared from 0.1 mole of crude I as described earlier[2] with reference to the tetrabromo analog. The product, obtained in 93% crude yield, was a tan, slightly sticky powder; as indicated by increased stickiness and formation of silver bromide, the salt deteriorates on standing and hence should be used as soon after preparation as possible.

threo-1,8,9-Tribromoheptadecane (III) was prepared under conditions found[14] to give optimum yields of 1-bromoheptadecane from silver stearate. A slurry of 50.0 g. (0.091 mole) of II in dry carbon tetrachloride was cooled to 0° and treated while stirring with 96 g. of a 15.2-weight % solution of bromine in the same solvent (total bromine added: 14.6 g., 0.091 mole). About 15–20% of the total expected carbon dioxide was collected during this stage. The cooling bath was then replaced by a steam bath; gas evolution was complete by the time the solution reached the boiling point, with 75–85% of the theoretical quantity of carbon dioxide being evolved (including that collected at 0°).

The reaction products were separated by chromatography on a 7.4 (diam.) × 20.5 cm. column of silicic acid (J. T. Baker reagent powder) prewashed as described earlier[2] and developed with 1.75 column-volumes each of 60–70° petroleum ether, 30% (by volume) benzene in petroleum ether, and absolute ethyl ether; yields: 52–53% III, 6–7% ester, and 26–36% recovered acidic material. A rechromatographed sample of III (eluted with *n*-pentane) was a pale yellow oil, $n_D^{25.0}$ 1.5065, $d^{21.2}$ 1.384.

Anal. Calcd. for $C_{17}H_{33}Br_3$: C, 42.78; H, 6.97; Br, 50.24. Found: C, 42.89; H, 6.75; Br, 50.22.

cis-1-Bromo-8-heptadecene (IV). The debromination of 10.4 g. (0.021 mole) of III in 20 ml. of benzene with 8.0 g. (0.12 mole) of activated 20-mesh granulated zinc in 25 ml. of ethanol proceeded readily, as judged by spontaneous reflux during the addition of the tribromide, and was completed by heating for an additional 15 min. Distillation of the product gave 5.65 g. (85%) of faintly yellow oil, b.p. 136–146° at 0.2 mm., the latter 4.55 g. of which (b.p. 140–146°) was reserved for subsequent steps and characterization; n_D^{25} 1.4704, d^{24} 1.018, infrared absorption at 10.3μ indicative of the presence of about 20% of the *trans*- isomer of IV.[15]

Anal. Calcd. for $C_{17}H_{33}Br$: C, 64.34; H, 10.48; Br, 25.18. Found: C, 64.20; H, 10.59; Br, 25.07.

Some improvement in the geometric homogeneity of IV was realized by low temperature crystallization from acetone (20% solutions), the higher melting, less soluble *trans*-material being concentrated in the precipitates, which were discarded. Thus 8.3 g. of crude IV (25% *trans*) after 5 hr. at −40° gave 7.2 g. 20% *trans;* a second application of the procedure (1 hr. at −60°) gave 4.74 g. 10% *trans*, b.p. 134.0–136.5° at 180 μ, n_D^{25} 1.4708, which was employed in preparation of the Grignard reagent (see below).

trans-1-Bromo-8-heptadecene was obtained by similar low temperature crystallization of a sample of crude IV (40% *trans*) prepared from a commercial sample of oleic acid later shown to contain rather large amounts of elaidic acid. The crystalline bromide (m.p. −9°, b.p. 115–125° at 100–125μ, n_D^{25} 1.4691, d^{27} 1.001) gave an infrared spectrum indicating 95% *trans*- component.

Oleic-1-C^{14} acid. Magnesium turnings (97.1 mg., 4.00 mmoles) were dried in the reaction vessel[2] by pumping down to 0.03μ, and the system was then filled with dry, oxygen-free nitrogen (tank gas passed through Fieser's solution,[17] Drierite, and a liquid nitrogen trap). The stirrer was started and a few milliliters of a solution of 1.1662 g. (3.67 mmoles) of IV (10% *trans*) and 73.1 mg. (0.51 mmoles) of methyl iodide in 27 ml. of freshly distilled, dry ethyl ether was added. With the vessel at room temperature the solution became hazy in 5–6 min., indicating that reaction had started; the remaining halide solution was then added dropwise over a 90-min. period. Stirring was continued for an additional 30 min. After the mixture had been let stand overnight, titration of a 1-ml. aliquot indicated formation of 3.47 mmoles of Grignard (83% on the basis of total halide employed). Essentially as described in detail earlier,[2] the remaining Grignard reagent (3.31 mmoles) was carbonated with the carbon dioxide from 746.1 mg. (3.782 mmoles) of barium carbonate containing 2.06 mc. C^{14}.

The reaction mixture was acidified and the products were taken up in *n*-pentane, washed with water, and freed of solvent, leaving a viscous yellow oil (0.98 g.) which was chromatographed on silicic acid to yield (in order of elution) 0.185 g. of hydrocarbon (presumably 9,25-tetratriacontadiene, formed from IV by a Wurtz-type reaction accompanying Grignard formation[2]), 0.025 g. of material of intermediate polarity, 0.65 g. of oleic-1-C^{14} acid (neut. equiv. 280; theory 282), and 0.06 g. of more strongly adsorbed material. The yield of oleic-1-C^{14} acid was 63.2% from IV (corrected for the aliquot of Grignard solution titrated) or 58.6% from $BaC^{14}O_3$.

Methyl oleate-1-C^{14} was prepared by treating the acid in ether with diazomethane; the crude product was purified by chromatography on a silicic acid column, yield 75%. The ester (counted as an "infinitely thick" sample after dilution with "cold" methyl oleate) had an activity of 1.71 mc./g. (calculated from the activity of $BaC^{14}O_3$ used as starting material, 1.84 mc./g.).

Because of the nature of the metabolism studies in which this ester was to be used, it was important to determine its content of methyl linoleate-1-C^{14} with some precision. A small sample of the ester which had been diluted about 3:1 with corn oil (for feeding experiments) was diluted further with about 10 parts of "cold" methyl linoleate,[18] and saponified to

(14) J. C. Nevenzel and D. R. Howton, unpublished.

(15) In view of the demonstrated good stereospecificity of the bromination-zinc-debromination of oleic acid[10] and the fact that elaidinization of linoleic acid (or of linolenic acid[14]) during an analogous decarboxylation-reconstitution[2] was not significantly greater than that routinely observed in its bromination-zinc-debromination, the rather extensive elaidinization of the *cis*-double bond in the present instance is noteworthy and probably attributable to the greater reactivity of the bromine substituents of its precursors. Racemization of the *threo*-dibromo grouping to *erythro* during treatment of the silver salt (II) with bromine is suspect; racemization of a reactive alkyl bromide under such circumstances has been reported.[16]

(16) C. L. Arcus, A. Campbell, and J. Kenyon, *J. Chem. Soc.*, 1510 (1949).

(17) L. F. Fieser, *Experiments in Organic Chemistry*, Part II, 2nd Ed., D. C. Heath and Co., New York, 1941, pp. 395–396.

(18) *Cf.* J. W. McCutcheon, *Org. Syntheses*, **22**, 75 (1942).

yield a mixture of fatty acids having a specific activity of 1695 d./sec./mg. Bromination of a 98.7-mg. sample of the fatty acid mixture in 3.5 ml. of *n*-pentane according to White and Brown[19] gave 83.85 mg. of crude *threo,threo*-9,10,12,13-tetrabromooctadecanoic acid (TBS) and showed the mixture to contain 89% linoleic acid. (Preliminary experiments with corn oil fatty acids and with linoleic acid[18] gave 65 and 95% linoleic acid, respectively, in good agreement with the expected values.) The crude TBS and successive recrystallized (from acetone) samples had specific activities of 92.1, 23.0, 18.3, and 17.0 d./sec./mg., the last corresponding to a linoleic acid content in the oleic-1-C^{14} acid of 1.90%.

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UNIVERSITY OF CALIFORNIA AT LOS ANGELES

(19) M. F. White and J. B. Brown, *J. Am. Oil Chem. Soc.*, **26**, 385 (1949).

Diels-Alder Reactions of *o*-, *m*-, and *p*-Nitrostyrene[1]

SARA JANE RHOADS, CHARLES B. HOPKINS AND VIRGINIA M. HYLTON

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The electrophilic properties of 2- and 4-vinylpyridine and of the electronically similar *o*- and *p*-nitrostyrene have been amply verified in recent years. Thus, it has been shown that these compounds readily undergo Michael-type addition at the double bond with a wide variety of nucleophiles.[2] That this behavior may be traced directly to the conjugation of the ethylenic linkage with the electronegative imino or nitro group is indicated by the lack of reactivity of 3-vinylpyridine and of *m*-nitrostyrene under the same conditions.[2a-c]

Although a detailed description of the mechanism of the Diels-Alder reaction is still lacking, it is generally assumed that the activity of the dienophile may be correlated with the degree of activation of the olefinic bond by electronegative groups acting through conjugation.[3] In view of these facts, it seemed reasonable to expect enhanced dienophilic properties in those vinyl aromatics for which electrophilic properties had been demonstrated.[2] Doering and Rhoads explored this possibility with 2- and 3-vinylpyridine[4]; their results, while confirming the activity of 2-vinylpyridine, also revealed 3-vinylpyridine as an equally effective dienophile. In order to test the generality of this lack of differentiation among position isomers, the study has now been extended to the nitrostyrene series.[5]

So that a direct comparison might be made in this series, a standard set of reaction conditions was used. Butadiene served as the reference diene in all cases. Preliminary runs indicated that a reaction temperature of 125° and a mole ratio of diene to dienophile of *ca.* 2.5 to 1 brought about appreciable reaction over a period of 20 to 40 hr. while minimizing the concurrent polymerization. Even so, the latter was appreciable and necessitated the development of isolation procedures which would assure the best yields of adducts. The thermal stability of the adducts under the reaction conditions was examined by heating them alone at 125° or higher for 40 hr.

The reaction of *p*-nitrostyrene and butadiene proceeded readily under the reaction conditions to yield the adduct, 4-(*p*-nitrophenyl)cyclohexene (Ia). The structural assignment is based on analysis and on reduction of the adduct to the known *p*-aminophenylcyclohexane (IIa). In Ia, as in the other adducts, the position of the double bond is assigned by analogy to the usual Diels-Alder result.

I a: *p*-nitro
b: *o*-nitro
c: *m*-nitro

II a: *p*-amino
b: *o*-amino
c: *m*-amino

Under the same conditions, *o*-nitrostyrene added butadiene to form 4-(*o*-nitrophenyl)cyclohexene (Ib). The latter, a low melting solid, was characterized as its dibromide, III. Catalytic reduction of Ib gave the known *o*-aminophenylcyclohexane (IIb).

m-Nitrostyrene has been prepared from the corresponding nitrocinnamic acid by a modification of the method of Wiley and Smith.[6a] By using a flash distillation technique[6b] to remove the styrene from the reaction flask, yields of 88% have been realized. The reaction of *m*-nitrostyrene and butadiene yielded the expected addition product, 4-(*m*-nitrophenyl)cyclohexene (Ic). On reduction, Ic absorbed four mole equivalents of hydrogen producing *m*-aminophenylcyclohexane (IIc), characterized as the benzenesulfonamide.

Under the standard reaction conditions of 40 hr. at 125°, the yields of purified, stable adducts, Ia, Ib, and Ic, were 60, 48, and 44%, respectively. Although such data are admittedly crude, it seems

(1) Abstracted from the M. S. theses of C. B. H. and V. M. H.

(2) (a) W. von E. Doering and R. A. N. Weil, *J. Am. Chem. Soc.*, 69, 2461 (1947); (b) H. B. Hass and M. L. Bender, *J. Am. Chem. Soc.*, **71**, 3482 (1949); (c) W. J. Dale and C. W. Strobel, *J. Am. Chem. Soc.*, **76**, 6172 (1954); (d) W. J. Dale and G. Buell, *J. Org. Chem.*, **21**, 45 (1956).

(3) K. Alder, C. V. Wilson, and J. A. VanAllan in *Newer Methods of Preparative Organic Chemistry*, Interscience Publishers, Inc., New York, N. Y., 1948, p. 399.

(4) W. von E. Doering and S. J. Rhoads, *J. Am. Chem. Soc.*, **75**, 4738 (1953).

(5) N. C. Deno and J. D. Johnston [*J. Am. Chem. Soc.*, **74**, 3233 (1952)] have reported the reactions of *o*-, *m*-, and *p*-nitrostyrene with sorbic acid, but under reaction conditions which make assessment of relative reactivity difficult.

(6) (a) R. H. Wiley and N. R. Smith, *J. Am. Chem. Soc.*, **70**, 2295 (1948); (b) *cf.* R. H. Wiley and M. H. Hobson, *ibid.*, **71**, 2429 (1949) who developed this technique for the preparation of the thermally sensitive *p*-formylstyrene.

clear that the reactivities of the isomeric nitrostyrenes in the Diels-Alder reaction do not show the *pronounced* difference which has been observed in the reactions of addition to the double bond proceeding by a simple ionic mechanism.[2c] As with the vinylpyridines,[4] there appears to be little parallelism between dienophilic and electrophilic reactivity in this series.

It is, tentatively, suggested that ionic forces, directly transmitted through a conjugated system to the reacting olefinic bond, are not of prime importance in determining the reactivity of the dienophile, and, by inference, the stability of the intermediate or activated complex. In harmony with Alder's empirical rule of "maximum accumulation of unsaturation,"[7] a more significant factor may be the mere presence of unsaturated centers and nonbonded electrons, which can, by orbital interaction, stabilize the reacting aggregate.[8,9]

EXPERIMENTAL[10]

Nitrostyrenes. The *o*- and *p*-nitrostyrenes were prepared by dehydrohalogenation of the corresponding nitrophenylethylbromides[11] according to the method of Strassburg, Gregg, and Walling.[12] Properties: *p*-nitrostyrene: yellow crystals, m.p. 20–21°, n_D^{20} 1.6074; *o*-nitrostyrene: heavy yellow oil, b.p. 60–62° at 0.1 mm., m.p. 11.5–12.0°, n_D^{20} 1.5783.

m-Nitrostyrene was prepared by the decarboxylation of *m*-nitrocinnamic acid in a modification of the Wiley-Smith method.[6a] By adapting the flash distillation technique[6b] to this preparation a considerable improvement in yield has been realized. *m*-Nitrocinnamic acid (5.0 g.) and cupric acetate (0.1 g.) were dissolved in 45 g. of warm quinoline. The resulting solution was added dropwise to a 125-ml. distillation flask containing copper powder and maintained at 300–310° in a metal bath. The rate of addition was regulated so that the flask remained fairly dry. Fresh copper powder was added as the original copper became coated with polymer. The entire distillate was transferred to a flask containing one and one-half times the quantity of 2.5*N* sulfuric acid required to neutralize the quinoline. Direct steam distillation into a Dean-Stark tube gave *m*-nitrostyrene as a heavy oil which was washed with successive portions of cold 6*N* sulfuric acid, water and sodium carbonate solution. Distillation of the dried, neutral material gave 3.0 to 3.4 g. (78–88%) of *m*-nitrostyrene, b.p. 75–76° at 0.35 mm., n_D^{20} 1.5845; reported, b.p. 90–96° at 3.5 mm., n_D^{20} 1.5836.[6a]

General procedure for Diels-Alder reactions. Five grams (0.034 m.) of the nitrostyrene, 7 ml. (0.08 m.) of butadiene (Matheson, C.P. grade) and 0.1 g. of hydroquinone were sealed in a Pyrex bomb tube. The tube was placed in a furnace maintained at 125 ± 2° for a period of 40 hr., after which it was cooled in a dry ice bath and opened.[13] Excess butadiene was present in all cases. The tube contents were leached out with ether (or benzene) and the ether soluble portion was transferred to a distillation apparatus. Fractionation of the reaction products gave the dimer of butadiene (4-vinylcyclohexene), the unreacted dienophile, and the *ortho*- and *meta*- adducts. The *para*- adduct was more easily separated from the polymeric residue by extraction with ethanol or by vacuum sublimation.

4-(p-Nitrophenyl)cyclohexene (Ia). In the reactions with *p*-nitrostyrene, the reaction tube at the end of the heating period always contained a considerable quantity of sticky, yellow polymer which required extensive leaching with ether or benzene. Recovery of the unreacted styrene was prevented by its instability. The adduct could be sublimed from the solid residue remaining after removal of solvent and butadiene dimer. At a bath temperature of 93° and a pressure of 10 mm. the sublimate consisted of feathery, white flakes, m.p. 87.0–87.2°. Recrystallization of the crude adduct from ethanol afforded pure white plates, m.p. 87.2–87.5°.

Anal. Calcd. for $C_{12}H_{13}NO_2$: C, 70.9; H, 6.5; N, 6.9. Found: C, 70.7; H, 6.1; N, 6.4.

Under the standard conditions, the best yield of Ia obtained was 60% of the theoretical.

4-(o-Nitrophenyl)cyclohexene (Ib). The reaction mixture from the reaction of *o*-nitrostyrene and butadiene was ether-soluble but after removal of the butadiene dimer and unreacted nitrostyrene, a tarry polymer remained with the adduct. Molecular distillation at 0.2 mm. and a bath temperature of 90° permitted the separation of Ib as a heavy oil which solidified on cooling, m.p. (crude) 18–19°. Recrystallization of the crude adduct from ethanol in a dry ice bath gave fine, white crystals, m.p. 24–25°, after vacuum drying at 0°. For analysis, Ib was converted to the higher melting dibromo derivative, III. (*Vide infra.*) The best yield of Ib obtained under the standard conditions was 48% with a recovery of unreacted *o*-nitrostyrene of 13%.

4-(m-Nitrophenyl)cyclohexene (Ic). In the case of the *m*-nitrostyrene the reaction mixture was soluble in ether but still contained a dark, glassy polymer. The adduct was separated from the polymer by distillation at 125° and 0.6 mm. to give, after recrystallization from ethanol and vacuum drying at room temperature, colorless plates, m.p. 47.0–47.5°. The analytically pure sample melted at 47.4–47.6°.

Anal. Calcd. for $C_{12}H_{13}NO_2$: C, 70.9; H, 6.5; N, 6.9. Found: C, 71.0; H, 6.5; N, 7.4.

The best yield of Ic obtained under the standard conditions was 44% with a 43% recovery of unreacted *m*-nitrostyrene.

1,2-Dibromo-4-(o-nitrophenyl)cyclohexane (III). To a solution of 0.515 g. of Ib in 10 ml. of carbon tetrachloride was added dropwise and with cooling in an ice-salt bath, a solution of an equivalent quantity of bromine in carbon tetrachloride. Removal of the solvent left an oil which was triturated under hexane at dry-ice temperature to yield a crystalline dibromide, m.p. 88–91° (50% yield). Recrystallized from hexane as pale, yellow needles, it melted at 90.4–91.0°.

Anal. Calcd. for $C_{12}H_{13}Br_2NO_2$: C, 39.7; H, 3.6; N, 3.9; Br, 44.0. Found: C, 39.8; H, 3.7; N, 3.4; Br, 44.0.

4-Aminophenylcyclohexane (IIa). Reduction of 0.487 g. of Ia dissolved in ethanol was accomplished over Adams catalyst in a microhydrogenation unit. Hydrogen absorption amounted to 94% of the theoretical four mole equivalents. The amine was isolated as an oil in 86% yield and crys-

(7) K. Alder, M. Schumacher and O. Wolff, *Ann.*, 564, 79 (1949).

(8) *Cf.* H. Henecka, *Z. Naturforsch.*, 4b, 15 (1949); *C. A.*, 44, 1909 (1950).

(9) The inadequacy of the "ionic" mechanism for many Diels-Alder reactions has been pointed out by others in a different connection. See refs. 5 and 7.

(10) All melting points are corrected. The analyses were performed by the Clark Microanalytical Laboratory, Urbana, Ill.

(11) E. L. Foreman and S. M. McElvain, *J. Am. Chem. Soc.*, 62, 1435 (1940).

(12) R. W. Strassburg, R. A. Gregg, and C. Walling, *J. Am. Chem. Soc.*, 69, 2141 (1947).

(13) These conditions were selected as standard for the comparison of yields of adducts. Exploratory runs were made at other temperatures and for shorter times in order to determine the best set of conditions and to develop the most efficient method of working the reaction mixtures. The yields obtained in these preliminary runs are not considered reliable indications of relative reactivity and are not included here.

tallized from ethanol-water as colorless plates, m.p. 50.8–52.4°, reported m.p. 57°,[14] 54–55°.[15] IIa was converted to the acetyl derivative, m.p. 131.4–131.9°, reported, m.p. 130–131°[15]; and to the phenylthiourea derivative, m.p. from ethanol, 157.8–158.1°, reported, m.p. 163–164°,[15] 157–158°.[16]

2-Aminophenylcyclohexane (IIb). An ethanolic solution of 0.475 g. of Ib was catalytically reduced with Adams catalyst and absorbed four mole equivalents of hydrogen to furnish 0.39 g. (95%) of the crude amine, IIb. The amine was characterized as the acetyl derivative, colorless needles, m.p. 101.2–102°, reported, m.p. 101°,[14] 102–103°[15]; and as the benzoyl derivative, felted needles from hexane, m.p. 153.8–154.4°, reported, m.p. 154°.[14]

3-Aminophenylcyclohexane (IIc). Reduction of 3.0 g. of the *meta*- adduct Ic proceeded rapidly and quantitatively over Adams catalyst to furnish 75% of the purified amine, IIc, b.p. 123–125° at 1.5 mm. IIc was converted to the benzenesulfonamide in the usual way. Recrystallization from ethanol afforded colorless crystals, m.p. 128.0–128.2°.

Anal. Calcd. for $C_{18}H_{21}NO_2S$: C, 68.5: H, 6.7; N, 4.4. Found: C, 68.6; H, 6.6; N, 4.3.

Stability of the adducts. The thermal stability of the adducts, Ia, Ib, and Ic was established by heating them alone at 125° or higher for 40 hr. in sealed tubes. In each case, the adduct could be recovered essentially unchanged.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF WYOMING
LARAMIE, WYO.

(14) O. Neuhoeffer, *J. Prakt. Chem.*, **135**, 95 (1932); *Chem. Abstr.*, **26**, 2435 (1932).

(15) W. J. Hickinbottom, *J. Chem. Soc.*, 2646 (1932).

(16) N. Kursanoff, *Ann.*, **318**, 309 (1901); *J. Chem. Soc. (Abstr.)*, **82**, 20 (1902).

Ultraviolet Spectra of 2-Substituted Furans and 5-Substituted Methyl Furoates

DONALD G. MANLY[1] AND E. D. AMSTUTZ

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The recent synthesis of many furan compounds containing furan to heteroatom bonds[2] together with the few compounds for which spectra have been recorded has permitted a fairly complete compilation of ultraviolet spectral data for simple furan derivatives. The wave length maxima, log ϵ, and $\Delta\lambda$[3] values are recorded in Table I for the 2-substituted furans and in Table II for the methyl 5-substituted-2-furoates. In each table the corresponding benzene or methyl *p*-substituted benzoate $\Delta\lambda$ values are included and are designated as $\Delta\lambda_{Ph}$.

TABLE I

$x(C_4H_3O)$

x	λ_{max}(mμ)	log ϵ	$\Delta\lambda$[a]	$\Delta\lambda_{Ph}$[b]
H—	(208)	(3.9)	0	0
Br—	215.5	3.99	7.5	6.5[c]
MeO—	221.0	3.82	13.0	13.5[c]
C_6H_5O—	222.0	4.06	14.0	23.2
C_6H_5S—	241.5	4.21	33.5	28.3
$C_6H_5SO_2$—	249.5	4.13	41.5	32.8
MeOOC—	252.1	4.13	44.1	26.3

[a] $\lambda_{max} - \lambda$ where $\lambda = 208$. [b] $\lambda_{max} - \lambda$ where $\lambda = 203.5$.

TABLE II

$x(C_4H_2O)$COOMe

x	λ_{max} (mμ)	log ϵ	$\Delta\lambda$[a]	$\Delta\lambda_{Ph}$[b]
H—	252.1	4.13	44.1	26.3
Cl—	260.5	4.23	52.5	37.5[c]
$C_6H_5SO_2$—	261.7	4.33	53.7	39.0
Br—	264.1	4.23	56.1	41.5
MeOOC—	264.6[d]	4.19	56.6	38.5
C_6H_5O—	275.0	4.25	67.0	54.5
MeO—	279.0	4.10	71.5	53.0
C_6H_5S—	291.8	4.33	83.8	89.7
O_2N—	295.4	4.08	87.4	55.0

[a] $\lambda_{max} - \lambda$ where $\lambda = 208$. [b] $\lambda_{max} - \lambda$ where $\lambda = 203.5$. [c] Taken from Doub and Vandenbelt, ref. 3. [d] Taken from ref. 4.

To calculate $\Delta\lambda$ values it was necessary to assume a wave length maximum for furan of 208 which was obtained by extrapolation of the experimental curve. The extrapolation of the solvent spectrum appears to be valid since a vapor spectrum (max = 222) was obtained of almost identical shape.

The $\Delta\lambda$ value is a measure of the electronic interaction of the group with the aromatic system to which it is attached and may provide information of a sort not obtainable from a study of reaction rates, for example, since it does not involve polarization by a reagent. By first separating the substituents into those which are "*ortho-para*" directing and those which are "*meta*" directing and then arranging each group in order of increasing $\Delta\lambda$ the following series are obtained:

$$C_6H_5S > C_6H_5O \geq MeO > Br > Cl > H$$

$$NO_2 > MeOOC > C_6H_5SO_2 > H$$

These results agree qualitatively with the degree of directing power observed in various aromatic electrophilic substitution reactions.

In Table I the most significant differences in $\Delta\lambda$ and $\Delta\lambda_{Ph}$ are to be found in cases where the substituents are of the markedly electrophilic type (ϕ-SO_2— and MeO—CO—). These differences require the furan ring to be a stronger nucleophile than the benzene ring. The same conclusion is required by the fact that for the phenoxy group

(1) Taken from the Ph.D. thesis of Donald G. Manly, Quaker Oats Fellow in Organic Chemistry 1954–56. Present address, Research Laboratories, The Quaker Oats Company, Barrington, Ill.

(2) D. G. Manly and E. D. Amstutz, *J. Org. Chem.*, **21**, 516 (1956).

(3) The concept of $\Delta\lambda$ was introduced and applied to a few benzene derivatives by L. Doub and J. M. Vandenbelt, *J. Am. Chem. Soc.*, **69**, 2714 (1947). See also J. M. Vandenbelt, "Correlation of Ultraviolet Absorption and Chemical Structure of Benzenoid Compounds" A.D.M.A. Research and Development Section Meeting, Cleveland, 1950 and Hot Springs, 1955.

$\Delta\lambda_{Ph} > \Delta\lambda$. Table II demonstrates the conjugative interaction of the rings with the common carbomethoxy substituent, as modified by the substituents of Table I. In general, it is clear that the furan ring is more nucleophilic and less electrophilic than the benzene ring.

EXPERIMENTAL

Furan (Du Pont) on redistillation boiled at 31.5°.

2-Substituted furans were prepared by the methods previously reported.[2]

Methyl 5-chloro-2-furoate was prepared in 42% yield (m.p. 40–41°) by passing chlorine through rapidly stirred methyl 2-furoate at 150° for 3 hr.

Methyl 5-bromo-2-furoate and *methyl 5-methoxy-2-furoate* were prepared as previously reported.[2]

Methyl 5-nitro-2-furoate (m.p. 79–80°) was prepared by the usual method.[4]

Methyl 5-phenoxy-2-furoate was prepared by reaction of the acid[2] with diazomethane in 98% yield; b.p. 133–135°/0.3 mm.

Anal. Calcd. for $C_{12}H_{10}O_4$: C, 66.1; H, 4.62. Found: C, 66.1; H, 4.63.

Methyl 5-thiophenoxy-2-furoate was prepared by reaction of the acid[2] with diazomethane in 98% yield; b.p. 146–148°/0.5 mm. m.p. 39–40°.

Anal. Calcd. for $C_{12}H_{10}O_3S$: C, 61.5; H, 4.30. Found: C, 61.5; H, 4.36.

Phenyl 5-carbomethoxy-2-furyl sulfone was obtained in quantitative yield by reaction of methyl 5-thiophenoxy-2-furoate with excess 30% hydrogen peroxide in glacial acetic acid. Recrystallization from methanol-water gave white needles melting at 102–103°.

Anal. Calcd. for $C_{12}H_{10}O_5S$: C, 54.1; H, 3.79. Found: C, 54.1; H, 3.90.

Methyl benzoate b.p. 85°/15 mm. 220.8 mμ (4.08).

Methyl p-bromobenzoate m.p. 77–78°. 245.0 mμ (4.26).

Methyl p-anisate m.p. 47–48°. 256.5 mμ (4.43).

Methyl p-nitrobenzoate m.p. 95–96°. 259.0 mμ (4.12).

Dimethyl terephthalate m.p. 139–140°. 242.0 mμ (4.47).

Diphenyl sulfone m.p. 128–130°. 236.3 mμ (4.17).

Diphenyl sulfide b.p. 151–153°/15 mm. 231.8 (3.80), 250.4 (4.07), 275.0 (3.28).

Diphenyl ether b.p. 129.5°/12 mm. 226.7 mμ (4.01).

Methyl p-phenoxybenzoate. The *p*-phenoxy acid[5] (m.p. 158–159°) was prepared by carbonation of the Grignard reagent from *p*-bromophenyl phenyl ether (Eastman). Direct esterification of the acid followed by recrystallization from 95% ethanol gave the product m.p. 56–57°, 258.0 mμ (4.26).

Anal. Calcd. for $C_{14}H_{12}O_3$: C, 73.7; H, 5.30. Found: C, 73.5; H, 5.05.

Methyl p-thiophenoxybenzoate. p-Thiophenoxybenzoic acid[6] was prepared by adding a cold solution of diazotized *p*-aminobenzoic acid to a solution of thiophenol in dilute sodium hydroxide. A poor yield of the product was obtained which after several recrystallizations from 95% ethanol melted at 170–174°. Direct esterification followed by recrystallization from 95% ethanol gave the ester, m.p. 69–70°, 293.2 mμ (4.23).

Anal. Calcd. for $C_{14}H_{12}O_2S$: C, 69.0; H, 4.57. Found: C, 68.9; H, 4.74.

Phenyl p-carbomethoxyphenyl sulfone was prepared by the action of hydrogen peroxide on methyl *p*-thiophenoxybenzoate. The product was recrystallized from 95% ethanol, m.p. 145–146°, 242.5 mμ (4.29).

Anal. Calcd. for $C_{14}H_{12}O_4S$: C, 60.9; H, 4.38. Found: C, 60.8; H, 4.26.

Spectra were taken in 95% ethanol at a concentration of 10 mg./l. on a Warren Recording Spectrophotometer.

The vapor spectrum of furan was obtained by placing one drop of furan in the bottom of the dry cell and allowing about 10 min. for the vapor to reach equilibrium.

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WILLIAM H. CHANDLER CHEMISTRY LABORATORY
LEHIGH UNIVERSITY
BETHLEHEM, PA.

(4) B. T. Freure and J. R. Johnson, *J. Am. Chem. Soc.*, **53**, 1142 (1931).

(5) W. Langham, R. Q. Brewster, and H. Gilman, *J. Am. Chem. Soc.*, **63**, 545 (1941).

(6) W. S. Weedon and H. W. Doughty, *Am. Chem. J.*, **33**, 424 (1905).

Synthesis of Xanthurenic Acid-4-C^{14}

MORTON ROTHSTEIN[1]

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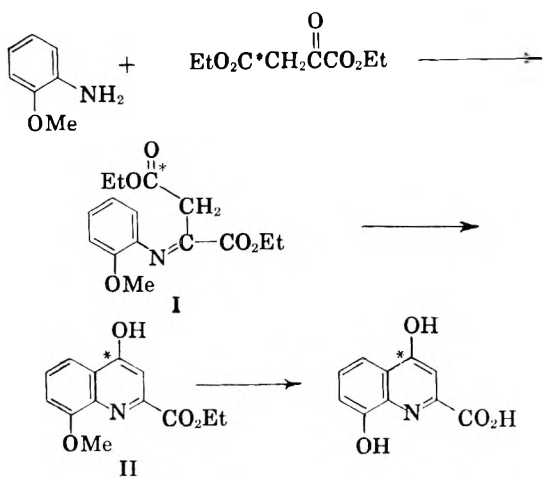
Xanthurenic acid has been known for some time as a tryptophan metabolite in mammals. In order to study the metabolism of this compound, it was desirable to incorporate a radioactive carbon atom into the molecule. A small scale synthesis (7mM) of xanthurenic acid-4-C^{14} was therefore undertaken utilizing the general procedure of Furst and Olsen[2]:



Numerous changes in the original procedure had to be made in order to provide a simple, continuous synthetic pathway starting from relatively inexpensive sodium acetate-1-C^{14}. These changes have more than doubled the over-all yield of xanthurenic

(1) This work was supported by a research grant from the Hobson Fund to the Cancer Research Institute, School of Medicine, University of California.

(2) A. Furst and C. J. Olsen, *J. Org. Chem.*, **16**, 412 (1951).

acid. The increase in yield appears to be primarily due to a new method for preparing the anil, I. A solution of *o*-anisidine and ethyl oxaloacetate in ether was refluxed in a Soxhlet extractor using calcium hydride in the extraction thimble, so that the hydride continuously removed the water produced by anil formation. For comparative yields, a preparation of ethyl oxaloacetate (synthesized from ethyl acetate and ethyl oxalate) was divided into two parts, and one part run as originally described[2] (refluxing benzene over Na_2SO_4) and one part as described above. Cyclization of the anils without isolation gave yields of 20% and 50%, respectively, of the ester, II, based on ethyl acetate.

It was found that hydrolysis of the ester, II, did not take place effectively, at least on this small scale, using the proportions of potassium iodide and 95% phosphoric acid recommended.[2] However, by increasing the relative amount of phosphoric acid, a nearly quantitative yield of xanthurenic acid was obtained from II.

EXPERIMENTAL

Preparation of ethyl oxaloacetate-4-C^{14}. Ethyl acetate-1-C^{14}, prepared in approximately 86% yield from 588 mg. (7.17 mM., 4.8 mc.) of sodium acetate-1-C^{14} essentially by the method of Ropp,[3] was mixed with 0.825 ml. of diethyl oxalate in 2 ml. of dry ether. This solution was added dropwise with stirring to a cooled (ice bath) suspension of sodium ethoxide (from 153 mg. of sodium hydride and 0.356 ml. of absolute ethanol) in 2 ml. of dry ether. The mixture was stirred in the cold for 2 hr. and then allowed to stand overnight at room temperature. The resulting grey paste was treated with a solution of 3 ml. of 6N H_2SO_4 in 10 ml. of water, and then was extracted 4 times with ether. The combined ether extracts which contained the ethyl oxaloacetate-4-C^{14} were dried over Na_2SO_4.

Formation of the anil (I). To the ether solution of ethyl oxaloacetate-4-C^{14}, still over Na_2SO_4, was added 1.2 ml. of freshly distilled *o*-anisidine. A precipitate of *o*-anisidine hydrosulfate was formed, presumably because of a small amount of H_2SO_4 carried over from the extraction procedure. The salt was removed by filtration, along with the Na_2SO_4. The yellow filtrate was evaporated to a volume of about 20 ml. and transferred to a micro Soxhlet extraction apparatus.[4] The thimble (10 × 50 mm.) was half filled with calcium hydride which had been ground in a mortar, and the apparatus was protected from the atmosphere with a drying tube. After being refluxed for 12 hr. the ether solution was washed with a solution of 1 g. of citric acid in 15 ml. of water in two portions, and then with water. The ether layer was dried (Na_2SO_4) and distilled to a small volume. It was then transferred to a 15 ml. pear shaped flask[5] and the last of the ether was removed by gentle distillation, and finally under vacuum. The yellow oil which remained was presumably the anil of *o*-anisidine and ethyl oxaloacetate.

Ethyl 4-hydroxy-8-methoxy quinaldate-4-C^{14} (II). To the material in the flask was added 3.5 ml. of Dowtherm A, and a small carborundum boiling chip. A reflux condenser was set in place and the flask immersed in an oil bath at 270–280° for 11 min. (Small differences in time apparently do not affect the yield adversely.) The resulting dark brown liquid was cooled and transferred to a separatory funnel with the aid of several ml. of ether. It was extracted 4 times with a total of 6 ml. of 6*N* HCl in 25 ml. of water. The light yellow HCl extracts were washed with ether and the ether layer was discarded. The acid solution was then filtered and carefully made just alkaline with finely powdered sodium carbonate. The resulting mixture was placed in a refrigerator for 3 hr. and the precipitate filtered, washed with water, and dried *in vacuo* over P_2O_5. The yield of ester was 0.72 g. or 40.5% based on sodium acetate-1-C^{14}.

Xanthurenic acid-4-C^{14}. The ester was placed in a 20 ml. pear shaped flask, and 11.3 g. of 95% phosphoric acid was added, followed by 7.2 g. of KI. After refluxing in an oil bath at 260° for 1.5 hr. the mixture was cooled and transferred to a 125 ml. Erlenmeyer flask with the aid of 50 ml. of water. The contents of the flask were heated gently and stirred until the black color had disappeared and a bright yellow precipitate remained. The mixture was placed in a refrigerator for several hours, and the yellow solid filtered onto a sintered glass funnel. The product was washed with water and then with alcohol. The crude xanthurenic acid-4-C^{14} was passed through the filter with dilute aqueous NaOH. The filtrate was acidified with dilute HCl and the precipitate collected as above. The process was repeated once again, and the product finally dried *in vacuo* over P_2O_5. The yield of xanthurenic acid-4-C^{14} was 0.58 g., or 39% based on sodium acetate-1-C^{14} (97% from the ethyl quinaldate).

Purity: Paper chromatographs in two solvents (butanol:acetic acid:water-5:1:4 and methanol:benzene:butanol:water-4:2:2:2) each showed only one spot when examined under ultraviolet light. These spots corresponded exactly to the only spot obtained radioautographically on x-ray film, and the R_f values agreed closely with those reported by other workers. The specific activity of the xanthurenic acid-4-C^{14} was 3.4 μc/mg. (Calcd.: 3.4 μc/mg.).

Department of Physiological Chemistry
School of Medicine, University of California
Berkeley 4, Calif.

(3) G. A. Ropp, *J. Am. Chem. Soc.*, 72, 2299 (1950).
(4) Corning Glass Co., Corning, N. Y.
(5) Metro Industries, Inc., Long Island City, N. Y.

New Synthesis of Aryl Esters of Aromatic Acids

Wm. H. Coppock

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It has been shown by several workers[1–6] that the aluminum chloride catalyzed reaction of alkyl chloroformates with aromatic hydrocarbons behaves in an abnormal manner. Alkylation of the hydrocarbon results instead of formation of the expected alkyl ester of the aromatic acid.

This note describes experiments in which aryl chloroformates react with aromatic hydrocarbons in the presence of aluminum chloride to form the expected aryl esters of aromatic acids.

(1) C. Friedel and J. M. Crafts, *Compt. rend.*, 84, 1450 (1877).
(2) C. Friedel and J. M. Crafts, *Ann. chim. phys.*, (6) 1, 527 (1884).
(3) E. H. Renne, *J. Chem. Soc.*, 41, 33 (1882).
(4) F. Kunckell and G. Ulex, *J. prakt. Chem.*, 86, 518 (1912).
(5) F. Kunckell and G. Ulex, *J. prakt. Chem.*, 87, 227 (1913).
(6) Buu-Hoï and J. Janicaud, *Bull. soc. chim. France*, 12, 640 (1945).

EXPERIMENTAL

Materials. The aryl chloroformates were synthesized in this laboratory by the method of Raiford and Inman.[7] The aromatic hydrocarbons used were Eastman grade. The aluminum chloride was Baker and Adamson, anhydrous, Reagent grade.

Phenyl benzoate. A mixture of 2.0 g. (0.0128 mole) of phenyl chloroformate, 1.75 g. (0.013 mole) of aluminum chloride and 10 cc. of dry benzene was heated on the steam bath under reflux for 1 hr. At the end of this time the evolution of gaseous hydrogen chloride had practically ceased. In all the preparations described it was assumed that the reaction was complete when gas was no longer evolved from the reaction mixture. After cooling to room temperature the reaction mixture was added slowly with stirring to an excess of ice-cooled dilute hydrochloric acid solution. After decomposition of the complex was complete the benzene layer was washed with water and then 5% sodium hydroxide solution. No appreciable precipitate formed when the alkaline extract was acidified. This was an indication that the aryl ester had not undergone the Fries rearrangement to form a hydroxyaryl ketone. The benzene was removed by steam distillation. The nonvolatile oil solidified when the water-oil mixture was cooled in ice, m. p. 66–68°. A mixed melting point of this product with a known sample of phenyl benzoate showed no depression. The yield was 1.62 g. (64%).

p-Chlorophenyl benzoate. A mixture of 3.82 g. (0.020 mole) of *p*-chlorophenyl chloroformate, 3.0 g. (0.0225 mole) of aluminum chloride and 20 cc. of dry benzene was refluxed on the steam bath for 5 hr. The reaction product was decomposed with cold dilute hydrochloric acid as previously described. To aid in solubilizing the product in the benzene layer 20 cc. of diethyl ether was added The benzene-ether layer was extracted with 5% sodium hydroxide solution and then washed with water. After removal of the benzene and ether by steam distillation the nonvolatile oil solidified when the water-oil mixture was cooled to room temperature. The crude product was crystallized from ethyl alcohol using charcoal, m.p. 88–89°. The yield was 2.7 g. (58%). There was no depression of the melting point when the product was mixed with a known sample of *p*-chlorophenyl benzoate which had been prepared by the Schotten-Baumann reaction.

p-Phenylphenyl benzoate. A mixture of 11.6 g. (0.05 mole) of *p*-phenylphenyl chloroformate, 8.0 g. (0.06 mole) of aluminum chloride and 30 cc. of dry benzene was heated on the steam bath under reflux for 45 min. The cooled reaction mixture was poured, with stirring, into an excess of cold dilute hydrochloric acid. A rather viscous mass resulted after stirring for 5 hr. After steam was passed through this mixture to remove excess benzene the nonvolatile oily residue solidified when cooled to room temperature. The crude product was crystallized from ethyl alcohol, m.p. 147–148°. A mixed melting point with a known sample of *p*-phenylphenyl benzoate showed no depression. The yield was 7.0 g. (51%).

Anal. Calcd. for $C_{19}H_{14}O_2$: C, 83.21; H, 5.11. Found: C, 83.23, 83.10; H, 5.08, 4.96.

p-Phenylphenyl p-toluate. A mixture of 11.6 g. (0.050 mole) of *p*-phenylphenylchloroformate, 8.0 g. (0.06 mole) of aluminum chloride and 35 cc. of dry toluene was refluxed for 1 hr. on the steam bath. The cooled reaction mixture was decomposed with dilute hydrochloric acid. After removing the excess toluene by steam distillation it was found that the nonvolatile oil solidified when the water-oil mixture was cooled. This solid was extracted with diethyl ether and the ethereal solution dried with potassium carbonate. The product resulting from the removal of the ether was crystallized from ethyl alcohol, m.p. 131–133°. The yield was 4.2 g. (30%). *p*-Phenylphenol and *p*-toluic acid were identified as the products of hydrolysis of the above substance with alcoholic potassium hydroxide.

(7) L. C. Raiford and G. O. Inman, *J. Am. Chem. Soc.*, 56, 1586 (1934).

Anal. Calcd. for $C_{20}H_{16}O_2$: C, 83.33; H, 5.56. Found: C, 83.19, 83.18; H, 5.26, 5.38.

Acknowledgment. The author is very grateful to the National Science Foundation for financial support of this investigation.

DEPARTMENT OF CHEMISTRY
DRAKE UNIVERSITY
DES MOINES, IOWA

Degradation of 3α,17α,21-Trihydroxypregnan-20-one-C^{14} Biosynthesized from Acetate-1-C^{14} by a Cushing's Patient[1,2]

ELIAHU CASPI, FRANK UNGAR, AND RALPH I. DORFMAN

Received July 9, 1956

In a previous communication[3] we reported the distribution of radioactivity in carbons 20 and 21 of cortisol-C^{14} biosynthesized from acetate-1-C^{14} by perfusion of the isolated calf adrenal gland. It was found that carbon 20 was derived from the carboxyl carbon and carbon 21 from the methyl carbon of acetate. This finding agreed with the scheme of Woodward and Bloch[4] for the incorporation of acetate into cholesterol. This communication deals with a similar study on a C^{14}-labeled adrenocortical steroid isolated from the urine of a human following the administration of acetate-1-C^{14}.[5]

Since there was not sufficient nonlabeled material available to serve as carrier for the degradation, the radioactive steroid, 3α,17α,21-trihydroxypregnan-20-one, was diluted with a related substance with a dihydroxy acetone side chain, 17α,21-dihydroxy-4-pregnene-3,20-dione. The mixture of 3α,17α,21-trihydroxypregnan-20-one-C^{14} and 17α,-21-dihydroxy-4-pregnene-3,20-dione had a corrected specific activity of 80.5 × 10^3 counts/min./mM. The mixture was reduced with sodium borohydride and subsequently oxidized with periodic acid to

(1) These studies were aided in part by Contract No. AT(30-1)-918, U. S. Atomic Energy Commission, by Contract No. DA-49-007-MD-184, Medical Research and Development Board, Office of the Surgeon General, Department of the Army, and by Grant No. EDC-38 from the American Cancer Society.

(2) Permission was granted by the Atomic Energy Commission to administer 2 mc of acetate-1-C^{14} to a female patient in the terminal stages of adrenal cortical carcinoma. The cooperation of George W. Thorn and staff at the Peter Bent Brigham Hospital, Boston, is gratefully acknowledged.

(3) E. Caspi, G. Rosenfeld, and R. I. Dorfman, *J. Org. Chem.*, 21, 814 (1956).

(4) R. B. Woodward and K. Bloch, *J. Am. Chem. Soc.*, 75, 2023 (1953).

(5) F. Ungar and R. I. Dorfman, Abst. Endocrin. Soc. Meeting, June 7–9, 1956, Chicago, Ill.

yield formaldehyde from C-21 and formic acid from C-20. The formaldehyde was precipitated as formadone and the formic acid was oxidized with mercuric oxide to carbon dioxide. The carbon dioxide was trapped in carbonate-free sodium hydroxide and subsequently precipitated as barium carbonate. No significant counts could be detected in the formadone which indicated that less than 50 counts/min./mM could have been present. On the other hand, 7.77×10^3 counts/min./mM were found in the barium carbonate.

The distribution of radioactivity in carbons 20 and 21 in 3α,17α,21-trihydroxypregnan-20-one-C^{14} agrees with that obtained in cortisol-C^{14} by calf adrenal perfusion.[3] On the basis of the scheme postulated by Woodward and Bloch[4] we would expect ten radioactive carbons to be incorporated into the first 21 carbons of cholesterol from acetate-1-C^{14}. If one assumes that corticosteroids are biosynthesized from acetate-1-C^{14} through cholesterol then the arrangement of all carbons of C^{14} atoms in corticosteroids would be expected to be the same as that found in the first 21 carbons of cholesterol. The present findings support the view that the carboxyl and the methyl carbons of acetate are incorporated into carbon 20 and 21, respectively, of a corticosteroid. The distribution of methyl and carboxyl carbons in the corticoid side chain is identical to that of carbons 20 and 21 of cholesterol.

EXPERIMENTAL

The specific activities were determined by the method of Karnovsky *et al.*[6] using a Robinson proportional counter.

Isolation and purification of C^{14}-labeled 3α,17α,21-trihydroxypregnan-20-one. Following the administration of 2 mc. of 1-C^{14}-acetate to a female patient[7] the urine was collected for 5 days.[5] The urine was hydrolyzed with β-glucuronidase and extracted with ethyl acetate. The ketonic fraction, prepared by a modified Girard separation,[7] was chromatographed on a silica gel column. The crystalline material eluted with benzene-ethyl acetate (3:1) was rechromatographed in the same system. Repeated recrystallization from acetone and finally ethanol gave crystals melting at 197–204° with a constant specific activity.

Specific activity determination of carbons 20 and 21. Chromatographically pure unlabeled 17α,21-dihydroxy-4-pregnene-3,20-dione (211 mg.) was added as carrier to the C^{14}-labeled 3α,17α,21-trihydroxypregnan-20-one (32.6 mg.) described in the section above. The specific activity of the mixture was 80.5×10^3 counts/min./mM. A 103 mg. portion of the mixture was dissolved in 15 ml. of methanol and stirred overnight at room temperature with 500 mg. of sodium borohydride. Water was added and following acidification with hydrochloric acid the mixture was extracted with ethyl acetate. The extract was washed with water, a saturated solution of sodium bicarbonate, water, dried over sodium sulfate, and taken to dryness *in vacuo*. The residue (108 mg.) was dissolved in 25 ml. of carbon dioxide–free ethanol, 36 ml. of a stock periodate solution were added and the solution was left for 135 min. at room temperature in the dark. The stock periodate solution was prepared by dissolving 1 g. of sodium metaperiodate in 70 ml. of water, adjusting the *p*H to 4 with 2*N* sulfuric acid, and making up the volume to 100 ml. The reaction mixture was distilled *in vacuo* to dryness and the distillate was collected in two flasks cooled with a dry ice–acetone mixture. The contents of both flasks were combined (80 ml.).

Oxidation of formic acid to carbon dioxide. A portion of the distillate (55 ml.) was flushed for 5 min. with oxygen to expel carbon dioxide; 2 g. of red mercuric oxide were added, the oxygen stream continued, and the mixture boiled for 30 min. The evolving gases were collected through a reflux condenser into two traps containing carbon dioxide-free sodium hydroxide. The collected carbon dioxide was precipitated as barium carbonate[8] and counted.

Precipitation of formadone. To a portion (25 ml.) of the distillate obtained following periodic oxidation, 1 ml. of glacial acetic acid was added and the solution was buffered with 300 mg. of sodium acetate. The formaldehyde was precipitated with dimedone[9] and the crystals collected, m.p. 193–194°. The formadone was recrystallized from methanol to a constant specific activity.

For the specific activity determinations blank experiments were carried out and the appropriate corrections were introduced.

Acknowledgment. We are indebted to Dr. M. L. Karnovsky of Harvard Medical School for his valuable suggestions and permission to use his counting equipment.

WORCESTER FOUNDATION FOR EXPERIMENTAL BIOLOGY, SHREWSBURY, MASS.

(6) M. L. Karnovsky, J. M. Foster, L. I. Gidez, D. D. Hagerman, C. B. Robinson, A. K. Solomon, and C. A. Villee, *Anal. Chem.*, 27, 852 (1955).

(7) J. J. Schneider, *J. Biol. Chem.*, 194, 338 (1952); 183, 365 (1950).

(8) M. Calvin, C. Heidelberger, J. C. Reid, B. M. Tolbert, and P. E. Yankwich, *Isotopic Carbon*, John Wiley & Sons Inc., N. Y., 1949, p. 84.

(9) E. Müller, editor, *Methoden der Organischen Chemie, Georg Thieme Verlag, Stuttgart, 1953*, Vol. 2, 456.

Electrical Effect of the Triphenylmethyl Group on an Aromatic Ring

ROBERT A. BENKESER AND REX B. GOSNELL

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The rates of the reactions of *meta*- and *para*-tritylbenzoic[1] acids with diphenyldiazomethane and those of *meta*- and *para*-tritylphenoxides with ethyl iodide have been obtained. These were treated in the usual manner to obtain the values of Hammett's "Substituent Constant[2] (σ)" for the triphenylmethyl group.

The *meta*- and *para*-tritylbenzoic acids were obtained by the oxidation of the corresponding tolyl compounds.[3]

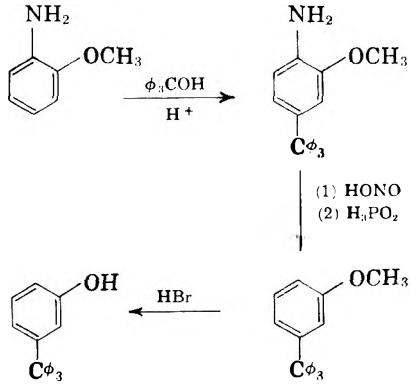
Para-tritylphenol was prepared by the tritylation of phenol. *Meta*-tritylphenol was synthesized

(1) "Trityl" has been used as a trivial name for the triphenylmethyl group.

(2) L. P. Hammett, *Physical Organic Chemistry*, McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 184.

(3) R. A. Benkeser and R. B. Gosnell, *J. Am. Chem. Soc.*, 78, 4914 (1956).

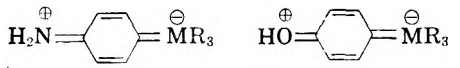
rather indirectly by the tritylation of *o*-anisidine, followed by deamination to give *m*-tritylanisole. The ether was then cleaved with hydrobromic acid to give the desired phenol.



The rates of the reaction of the benzoic acids with diphenyldiazomethane were followed spectrophotometrically,[4] while those of the phenoxides with ethyl iodide were determined titrimetrically.[5]

Assuming no resonance effects the almost identical values for σ_m and σ_p clearly indicate that the electrical effect of the triphenylmethyl group on an aromatic ring is small.

Earlier work from this laboratory[5] demonstrated that silicon and germanium atoms are capable of valence shell expansion when conjugated with strong electron-supplying groups like amines or phenols.



M = Si or Ge

This was indicated by the distinctly positive value of the expression[6] $\sigma^* - \sigma_p$ for the R_3Si- and R_3Ge-groups.

It is well known that carbon cannot expand its valence shell. This is nicely corroborated by the $\sigma^* - \sigma_p$ expression for the trityl group which in this instance is somewhat negative.

Sufficient data are not available to justify comment concerning the negative sigma values obtained in the *meta*- and *para*-phenoxide reactions. Additional cases must be studied to determine whether the slight electron supplying ability which these values indicate is real.

One can conclude, however, that both the triphenylsilyl and triphenylgermanyl groups are electron attracting in contrast to the trityl group which is essentially neutral. Apparently the electrical influence of the three phenyl groups is more pronounced when attached to silicon and germanium than to carbon.

TABLE I

RATE CONSTANTS FOR REACTION OF BENZOIC ACIDS WITH DIPHENYLDIAZOMETHANE IN ETHANOL AT 30°

Substituent	k_2(l./Mole Sec.) × 10^{-2}
m-CH_3	1.54
None	1.83
m-ϕ_3C	1.85
p-ϕ_3C	2.01
p-Cl	3.12
p-Br	3.21
p-NO_2	8.80

TABLE II

RATE CONSTANTS FOR REACTION OF SODIUM PHENOXIDES WITH ETHYL IODIDE IN ETHANOL AT 35°

Substituent	k_1(Sec.$^{-1}$) × 10^{-5}
m-CH_3	77.0
m-ϕ_3C	76.5
p-ϕ_3C	74.3
None	64.8
p-Br	36.3
m-Cl	29.0
p-NO_2	5.08

TABLE III

CONSTANTS FOR THE TRIPHENYLMETHYL GROUP

Reaction	ρ	log k_o[a]	r[b]	σ_p	σ_m
Sodium phenoxides with ethyl iodide	0.877	−3.194	0.02	−0.07	−0.09
Benzoic acids with diphenyldiazomethane	0.867	−1.717	0.02	0.02	−0.01

[a] The unit of time for all rate constants is seconds. [b] Median deviation of the sigma value.

It was hoped that these values for sigma might be useful in establishing the operation of a "bulk effect".[7] However since the electrical effect is so small, no interpretation can be made.

EXPERIMENTAL

p-Tritylphenol. This material was prepared as described by McKenzie and Chuchani.[8]

Tritylation of o-anisidine. The following materials were refluxed for 4 hr.: 7 g. (0.057 mole) of *o*-anisidine, 13 g. (0.050 mole) of triphenylcarbinol, 60 ml. of glacial acetic acid, and 5 ml. of concentrated hydrochloric acid. At the end of this time the solution was poured into water. The resulting solid was separated and dissolved in boiling pyridine. This solution was poured into water and the solid was recrystallized from 95% ethanol. Finally, sublimation gave *o*-methoxy-*p*-tritylaniline with a melting point of 185°–186°. The yield was 44%.

(4) J. D. Roberts, E. A. McElhill, and R. Armstrong, *J. Am. Chem. Soc.*, **71**, 2923 (1949).

(5) R. A. Benkeser, C. E. DeBoer, R. E. Robinson, and D. M. Sauve, *J. Am. Chem. Soc.*, **78**, 682 (1956).

(6) σ^* represents the σ_p value when the group in question is situated *para* to an amine or phenol. See H. H. Jaffe [*Chem. Revs.*, **53**, 225 (1953)] where this designation was introduced. The sigma constant of a group substituted in a para position to an electron withdrawing group, *e.g.* carboxyl, is designated simply as σ_p.

(7) C. C. Price and D. C. Lincoln, *J. Am. Chem. Soc.*, **73**, 5836 (1951).

(8) C. A. McKenzie and G. Chuchani, *J. Org. Chem.*, **20**, 342 (1955).

Anal. Calcd. for $C_{26}H_{23}NO$: C, 85.44; H, 6.35; N, 3.83. Found: C, 85.59; H, 6.46; N, 3.95.

m-Tritylanisole. The product from the tritylation of *o*-anisidine was deaminated by dissolving 4 g. of this material in 150 ml. of acetic acid and adding 120 ml. of 50% hypophosphorous acid. This clear solution was cooled to 0° and 4 g. of sodium nitrite was added. The mixture was allowed to stand for 2–3 hr. and thus reach room temperature. A solid precipitated which was removed by filtration and recrystallized from a mixture of toluene and petroleum ether. Sublimation gave *m*-tritylanisole with a melting point of 169°–170°. The yield was *ca.* 60%.

Anal. Calcd. for $C_{26}H_{22}O$: C, 89.10; H, 6.33. Found: C, 89.45; H, 6.60.

m-Tritylphenol. The ether prepared above was cleaved with hydrobromic acid in a conventional manner to yield *m*-tritylphenol with a melting point of 278°–280°. The infrared spectrum of this material had a fairly strong absorption peak at 12.8 μ, characteristic of a meta disubstituted benzene. The yield was ca. 60%.

Anal. Calcd. for $C_{25}H_{20}O$: C, 89.24; H, 5.95. Found: C, 89.11; H, 6.21.

Structure proof for m-tritylanisole. Aniline was tritylated in the usual way with *m*-methoxyphenyldiphenylcarbinol (from *m*-bromoanisole and benzophenone, *via* the Grignard reagent). The resulting *m*-methoxyphenyl-*p*-aminophenyldiphenylmethane was deaminated in the same manner described for *o*-methoxy-*p*-tritylaniline to give *m*-tritylanisole. The latter gave no depression in a mixed melting point with material obtained from the tritylation product of *o*-anisidine. The infrared spectra of the two materials were identical. Both could be cleaved to yield *m*-tritylphenol.

Tritylphenetoles. The tritylphenetoles were isolated from their respective reaction mixtures obtained from the rate studies. The *para*-ethyl ether melted at 189°–190°.

Anal. Calcd. for $C_{27}H_{24}O$: C, 88.97; H, 6.64. Found: C, 89.21; H, 6.76.

The *meta* ethyl ether melted at 139°–140°.

Anal. Calcd. for $C_{27}H_{24}O$: C, 88.97; H, 6.64. Found: C, 88.84; H, 6.60.

Acknowledgment. The authors are grateful to the National Science Foundation whose financial assistance made this work possible.

DEPARTMENT OF CHEMISTRY
PURDUE UNIVERSITY
LAFAYETTE, IND.

Reaction of Hydroxylamine with Ethyl α-(2,2,2-Trichloroethylidene)acetoacetate

M. L. WOLFROM, JACK RADELL,[1] AND R. M. HUSBAND[1]

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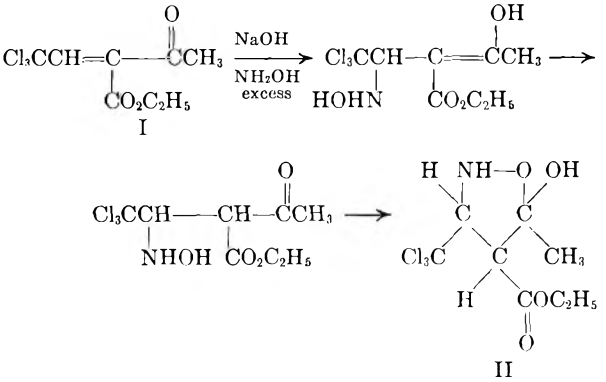
The preparation of ethyl α-(2,2,2-trichloroethylidene)acetoacetate (I) by the reaction of chloral with ethyl acetoacetate in the presence of acetic anhydride, was reported by Claisen and Matthews.[2]

$$Cl_3CCHO + H_2C(CO_2C_2H_5)COCH_3 \xrightarrow{Ac_2O} Cl_3CCH{=}C(CO_2C_2H_5)COCH_3 + H_2O$$

(1) Bristol Laboratories Research Associate (R. M. H.) and Research Fellow (J. R.) of The Ohio State University Research Foundation (Project 224).

(2) L. Claisen and F. E. Matthews, *Ann.*, **218**, 175 (1883).

We have found that the use of basic catalysts, to effect the condensation, results in considerably lower yields. In an effort to prepare an oxime of this substance, we obtained a crystalline derivative which exhibited the analysis required for an addition rather than a condensation reaction product. An infrared study of the hydroxylamine addition product showed no apparent carbon to carbon or carbon to nitrogen double bonds while the ethyl α-(2,2,2-trichloroethylidene)acetoacetate (I) did show a band (6.1 μ) for the carbon to carbon double bond. It was therefore concluded that no oxime was present in the reaction product but that a probable 1,4-addition of hydroxylamine to ethyl α-(2,2,2-trichloroethylidene)acetoacetate had occurred to form a single racemate of ethyl α-(2,2,2-trichloro-1-hydroxaminoethyl)acetoacetate. To our knowledge, such an exclusive addition of hydroxylamine to an α,β-unsaturated ketone is unique. The probable reactions occurring are shown below.



Ethyl α-(2,2,2-trichloroethylidene)acetoacetate (I) showed a rather broad and complex carbonyl band at 5.8 μ whereas its addition product with hydroxylamine exhibited a simple and very sharp carbonyl band at 5.7 μ. In the absence of predictable[3] evidence for both ester and ketonic (possibly enolized) bands in the final product, a cyclic structure (II) is suggested tentatively for it.

By arrangement with the Chemical-Biological Coordination Center, 2101 Constitution Ave., Washington 25, D. C., the trichloroketo ester and the hydroxamino ester, herein described, were tested for various types of biological activity, but no significant results were obtained.

EXPERIMENTAL

Ethyl α-(2,2,2-trichloroethylidene)acetoacetate (I). The method briefly described by Claisen and Matthews[2] was employed. A solution of 200 ml. (301 g. or 2 moles) of chloral, 254 ml. (260 g. or 2 moles) of ethyl acetoacetate and 190 ml. (204 g. or 2 moles) of acetic anhydride was refluxed for 18 hr. The ethyl α-(2,2,2-trichloroethylidene)acetoacetate distilled at 99–100° at 1 mm. on a 10-inch Widmer column; yield 203 g. (39% based on ethyl acetoacetate),

(3) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," Methuen Co., Ltd., London, 1954, p. 157.

n_D^{20} 1.4942, d_4^{15} 1.3420, d_4^{20} 1.2565. The only physical constant reported by Claisen and Matthews[2] was the density, with which our value is in exact agreement.

When piperidine was used in catalytic and 0.1 molar amounts, a product yield of 6% was obtained. Like results were observed on employing piperidine acetate in ethanol[4] as a catalyst.

Ethyl α-(2,2,2-trichloro-1-hydroxaminoethyl)acetoacetate (II?). To a solution of 1.3 g. (0.019 mole) of hydroxylamine hydrochloride in 3 ml. of water was added 2 ml. of 10% sodium hydroxide, 0.50 g. (0.0019 mole) of ethyl α-(2,2,2-trichloroethylidene)acetoacetate and enough ethanol (*ca.* 1 ml.) to dissolve the trichloro compound. The solution was refluxed for 10 min. on the water bath, cooled to room temperature, and 5 ml. of water added. The crystalline material that separated was recrystallized from 80% ethanol and from ethyl acetate; yield 0.45 g. (80%), m.p. 152–153°, iodoform test (+), ferric chloride (ethanol) enolic test (−), x-ray powder diffraction data: 7.00[6] −0.9,[6] 5.62–0.4, 4.69–1.0, 4.19–0.5, 3.80–0.6, 3.18–0.5, 2.85–0.5, 2.73–0.1, 2.53–0.2, 2.36–0.2, 2.20–0.8, 2.10–0.2, 1.96–0.1, 1.75–0.1.

Anal. Calcd. for $C_8H_{12}NO_4Cl_3$: C, 32.84; H, 4.13; N, 4.79; Cl, 36.36. Found: C, 32.51; H, 3.99; N, 4.74; Cl, 36.49.

An infrared spectrum of ethyl α-(2,2,2-trichloroethylidene)acetoacetate, in chloroform solution, showed the presence of a carbonyl group (5.8 μ) and a carbon to carbon double bond (6.1 μ). The infrared spectrum of ethyl α-(2,2,2-trichloro-1-hydroxaminoethyl)acetoacetate, in chloroform solution, showed the presence of a carbonyl group (5.7 μ) and no carbon to carbon or carbon to nitrogen double bond.

Acknowledgment. The authors are pleased to acknowledge the assistance of Dr. G. E. McCasland, in preparing the manuscript of this work for publication, and the counsel of Dr. M. P. Cava in interpreting the infrared data obtained.

Department of Chemistry
The Ohio State University
Columbus 10, Ohio

(4) R. Kuhn, W. Badstübner, and C. Grundmann, *Ber.*, 69, 98 (1936).

(5) Interplanar spacing, Å, CuK_α radiation.

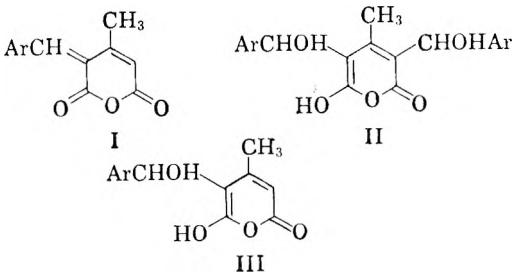
(6) Relative intensity by visual estimation; 1.0 most intense.

2-Pyrones. XXIV. Derivatives of α,β-Dimethylglutaconic Anhydride

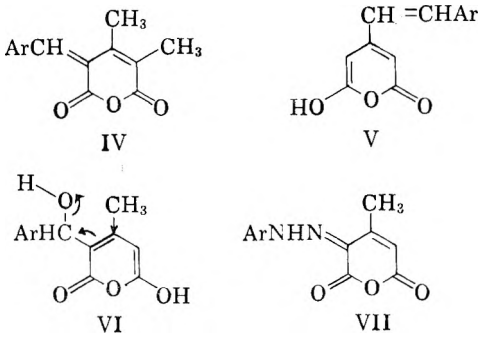
Richard H. Wiley and H. G. Ellert

Received July 12, 1956

As a part of a continuing study designed to provide additional information about the chemistry of β-methylglutaconic acid and its derivatives which are of current importance as intermediates in the biosynthesis of cholesterol[1] we have extended our previous studies[2,3] in which we noted differences in the behavior of glutaconic anhydride and β-methylglutaconic anhydride in their reactions with aromatic aldehydes. The ease of formation of the arylidene structure (I) from the β-methyl substituted anhydride was attributed to two possible factors: the steric inhibition of further condensation of the aldehyde in the α-position, leading to structures such as II, and increased ease of dehydration of the carbinol III as a result of the electron releasing characteristics of the β-methyl group. In order to evaluate the relative importance of these two factors we have studied the reaction of



α,β-dimethylglutaconic anhydride with aromatic aldehydes and diazonium salts. Using techniques described previously,[2-4] this anhydride condensed readily with aromatic aldehydes to give 24–39% yields of arylidene structures (IV). The data are summarized in Table I. Although a refined study



of the yields obtainable in these reactions was not made, it appears that this reaction, at least, shows no improvement over the reaction with β-methylglutaconic anhydride. From this it is concluded that the ease of dehydration of the carbinol, through the process illustrated in VI, is a more important factor in determining the course of this reaction than is further condensation of the aldehyde in the ortho position. The latter possibility, completely eliminated in the reaction of the α,β-dimethyl anhydride, results in no marked change in the character of the reaction. It is anticipated, therefore, that replacement of the β-methyl group with a more effective electron release group would result in a marked increase in the ease of formation of structures of the arylidene (I, IV) type.

There remains a possibility, not previously considered in this series, that the aldehyde con-

(1) H. Rudney, *J. Am. Chem. Soc.*, 76, 2595 (1954); 77, 1698 (1955); J. L. Rabinowitz *et al.*, *J. Am. Chem. Soc.* 77, 1295 (1955); 76, 3037, 5168 (1954); K. Bloch, L. C. Clark, and I. Harary, *J. Biol. Chem.*, 211, 687 (1954).

(2) Richard H. Wiley and H. G. Ellert, *J. Am. Chem. Soc.*, 77, 5187 (1955).

(3) Richard H. Wiley, E. L. DeYoung, and N. R. Smith, *J. Am. Chem. Soc.*, 76, 1675 (1954).

(4) Richard H. Wiley and C. H. Jarboe, *J. Am. Chem. Soc.*, 77, 403 (1955).

TABLE I

γ-ARYLIDENE-α,β-DIMETHYLGLUTACONIC ANHYDRIDES

Aryl Group	Color	M.P.,[a] °C.	Yield, %	Analysis Carbon % Calcd.	Carbon % Found	Hydrogen % Calcd.	Hydrogen % Found
p-Dimethylaminophenyl	Purple	237–239E	30	70.83	70.15	6.32	6.07
p-Diethylaminophenyl	Purple	163B	24	72.21	71.93	7.07	6.81
3,4-Dimethoxyphenyl	Yellow	159–160E	39	66.66	66.64	5.59	5.54
3,4-Diethoxyphenyl	Yellow	139–141B	37	68.34	67.98	6.37	6.23
1-Naphthyl	Orange	192–194E	33	77.68	77.77	5.07	4.80

[a] E, ethyl acetate; B, benzene.

densation takes place at the β-methyl group to give a structure V. In order for this reaction to occur the methyl group must be considered to be activated by the principle of vinylogy as one would expect the methyl group of ethyl crotonate or ethyl β,β-dimethylacrylate to be activated. Although there are analogies for such activation—for example, the base-catalyzed condensation of ethyl oxalate with ethyl crotonate to give diethyl oxaloacetate[5]—the analogy does not hold for the aldehyde condensations. It has been shown[6] that the base-catalyzed condensation between benzaldehyde and either crotonic acid or β,β-dimethylacrylic acid takes place at the α-carbon atom with rearrangement of the double bond. Thus, crotonic acid gives α-benzylidenevinylacetic acid. If such a reaction occurred with β-methylglutaconic anhydride, the accepted structure IV would result. At present there seems to be no more direct basis than this comparison for eliminating structure V. Positive identification of a band characteristic of the methyl group at 3.5 μ in the infrared is not practical because of the lack of resolution in this region using pellet techniques and the insolubility of the anhydride and its derivatives in solvents such as carbon disulfide and carbon tetrachloride which are transparent in this region. It is further interesting that apparently none of the known transformation and interconversions[7] of products obtained from this aldehyde-anhydride condensation can be used to clearly eliminate the possibility of structure V.

Coupling of α,β-dimethylglutaconic anhydride with a variety of aryldiazonium salts, using techniques previously described,[1–3] has given the γ-arylhydrazono derivatives (VII) listed in Table II.

EXPERIMENTAL

α,β-Dimethylglutaconic anhydride was prepared from the corresponding acid,[8] m.p. 103°, by cyclization with acetyl chloride on heating. In our hands the anhydride, b.p. 138–140°/3 mm, solidified, m.p. 38–42°, but could not be recrystallized. The derivatives listed in Tables I and II were prepared by procedures described in previous reports.[1–3]

TABLE II

γ-KETO-α,β-DIMETHYLGLUTACONIC ANHYDRIDE ARYLHYDRAZONES

Aryl Group	Color	M.p.,[a] °C.	Yield, %	Analysis Nitrogen % Calcd.	Nitrogen % Found
Phenyl	Orange	167–170H	49	11.47	11.50
p-Nitrophenyl	Yellow	214–218H	62	14.53	14.60
p-Tolyl	Yellow	177–178E	50	10.85	11.07
o-Anisyl	Orange	185–188F	29	10.21	10.31

[a] H, glacial acetic acid; E, ethyl acetate-petroleum ether; F, ethyl acetate or benzene.

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DEPARTMENT OF CHEMISTRY
COLLEGE OF ARTS & SCIENCES
UNIVERSITY OF LOUISVILLE
LOUISVILLE, KY.

(5) Richard H. Wiley and A. S. Hart, *J. Am. Chem. Soc.*, **76**, 1942 (1954).

(6) R. Kuhn and S. Ishikawa, *Ber.*, **64**, 2347 (1931); S. Ishikawa and R. Kojima, *Science Repts Tokyo Bunrika Daigaku*, **1**, 297 (1934); *Chem. Abstr.*, **28**, 2697 (1934).

(7) See for example V. Petrow and O. Stephenson, *J. Chem. Soc.*, 1310 (1950).

(8) N. Bland and J. F. Thorpe, *J. Chem. Soc.*, **101**, 1557 (1912).

Synthesis of 5,6,7-Trimethoxyindole, a Possible Intermediary Metabolite of Mescaline[1]

R. D. MORIN,[2] F. BENINGTON,[2] AND L. C. CLARK, JR.[3]

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The hypothesis that the currently designated psychotomimetic substances owe their unique physiological activity to an indole nucleus has been proposed by several investigators.[4–8] This has

(1) This research was supported by Battelle Memorial Institute funds and in part by Public Health Service Grant No. M-600(R).

(2) Battelle Memorial Institute.

(3) Fels Research Institute.

(4) H. Fabing, *Neurology*, **5**, 603 (1955).

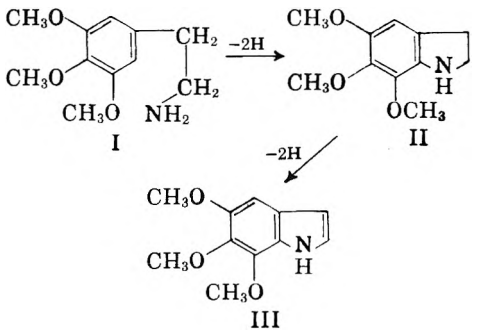
(5) A. Hoffer, H. Osmond, and J. Smythies, *J. Mental Sci.*, **100**, 29 (1954).

(6) A. S. Marazzi and E. R. Hart, *Science*, **121**, 365 (1955).

(7) D. W. Wooley and E. Shaw, *Science*, **119**, 587 (1954).

(8) F. Benington, R. D. Morin, and L. C. Clark, *J. Org. Chem.*, **20**, 1292 (1955).

stemmed from the fact that the psychotogens *d*-lysergic acid diethylamide, bufotenine, yohimbine, and adrenochrome contain an indole ring. To explain the psychotomimetic activity of β-phenethylamines such as mescaline (I), amphetamine, and 3,4,5-trimethoxyamphetamine in terms of this hypothesis, it would be necessary that these substances be capable of undergoing oxidative cyclization, *in vivo*, to the corresponding indoles. Opposed to this generalization is the fact that a number of indoles which are closely related to *d*-lysergic acid diethylamide (*e.g.* 2-bromo-*d*-lysergic acid diethylamide) fail to show psychotomimetic activity.[9] If these concepts are meaningful, it would be reasonable to expect that either 5,6,7-trimethoxyindole (III) or 5,6,7-trimethoxy-2,3-dihydroindole (II) would show psychotomimetic activity under proper physiological conditions.



The synthesis of the hitherto unknown indole (III) presented unexpected difficulties. Only one of seven alternate routes explored was found to be practical. The critical step in several of these routes was the introduction of a nitro group into the 2-position of a suitably 1-substituted-3,4,5-trimethoxybenzene. Finally, this step was solved when conditions were found for the nitration of 3,4,5-trimethoxy-β-nitrostyrene in acetic anhydride solution with red fuming nitric acid to give 2-nitro-3,4,5-trimethoxy-β-nitrostyrene in 9% yield. Reductive cyclization of this compound to 5,6,7-trimethoxyindole (III) was accomplished with iron powder and acetic acid in a manner similar to that described by Ek and Witkop.[10] Although the biological evaluation of this compound will require various pharmacological tests, preliminary results, involving the intravenous injection of large doses in cats, which show a dramatic reaction to mescaline, indicate that III is without observable action in terms of changes in behavior or brain oxygen tension. Further biological studies of the action of both II and III at appropriately selected metabolic sites will be necessary in order to ascertain whether mescaline acts through these indole intermediaries.

(9) E. Rothlin, paper presented at "Conference on the Pharmacology of Psychotomimetic and Psychotherapeutic Drugs," held in April 1956 at the New York Academy of Science.

(10) A. Ek and B. Witkop, *J. Am. Chem. Soc.*, **76**, 5583 (1954).

The synthesis of II is currently underway, since this compound would presumably be the primary *in vivo* oxidative cyclization product of mescaline.

EXPERIMENTAL[11]

2-Nitro-3,4,5-trimethoxy-β-nitrostyrene. A precooled solution (−8°) of 7.9 g. of 3,4,5-trimethoxy-β-nitrostyrene in 40 ml. of acetic anhydride was rapidly stirred during the dropwise addition of 5 ml. of red fuming nitric acid. The temperature of the nitration mixture was maintained at −7° to −8° during this phase of the reaction. Following the addition of the nitric acid, the nitration mixture was stirred for an additional 20 min. and then poured onto 200 ml. of an ice water mixture. Solid sodium carbonate was then added to the mixture to hasten the hydrolysis of the acetic anhydride. The crude precipitated nitro compound was collected on a filter, carefully washed with water and then recrystallized from aqueous ethanol. There was obtained 0.8 g. (9.4%) of 2-nitro-3,4,5-trimethoxy-β-nitrostyrene, m.p. 177–178°, as yellow needles.

Anal. Calcd. for $C_{11}H_{12}N_2O_7$: C, 46.5; H, 4.22; N, 9.85. Found: C, 46.7; H, 4.06; N, 9.56.

5,6,7-Trimethoxyindole (III). A solution of 2.5 g. of 2-nitro-3,4,5-trimethoxy-β-nitrostyrene in 18 ml. of ethanol was reduced with 8.8 g. of iron powder and 18 ml. of glacial acid in accordance with the procedure of Ek and Witkop.[10] After treating the reaction mixture with a solution of sodium bisulfite in 220 ml. of water, the crude indole was extracted with five portions of ether. Evaporation of the ether gave 1.4 g. of oily crude product which was taken up in a mixture of 15 ml. of dry benzene and 15 ml. of petroleum ether (30°–60°) and adsorbed on a column of 15 g. of chromatographic alumina. Treatment of the column with 36 ml. of the original benzene-petroleum mixture containing an additional 18 ml. of dry benzene was effective in selectively eluting the indole, since the tars and color bodies were more strongly adsorbed.

By evaporation of the eluate, there was obtained 0.9 g. of III, as a green oil which gradually solidified upon standing; the solid product melted at 70–72°. A colorless analytical specimen, m.p. 71–72°, was obtained by evaporative distillation at 0.4 mm.

Anal. Calcd. for $C_{11}H_{13}NO_3$: C, 63.8; H, 6.3; N, 6.8. Found: C, 63.7; H, 6.5; N, 6.7.

The ultraviolet spectrum in methanol–1-propanol showed λ_{max} (log ϵ) 268 (3.52); [287 (3.34)].

BATTELLE MEMORIAL INSTITUTE
COLUMBUS 1, OHIO

THE FELS RESEARCH INSTITUTE
YELLOW SPRINGS, OHIO

(11) All melting points are uncorrected.

Mescaline Analogs. VII. 3,4,5-Trimethyl-β-phenethylamine

F. BENINGTON,[1] R. D. MORIN,[1] AND LELAND C. CLARK, JR.[2]

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A mescaline analog in which each of the methoxyl groups at the 3,4, and 5- positions is replaced by methyl has not been reported previously. The

(1) Battelle Memorial Institute.

(2) Fels Research Institute.

effect of replacement of alkoxyl by methyl or ethyl has been studied in the case of the 2,4,6-substituted phenethylamines,[3] but all compounds in this series produced markedly different effects on the respiratory enzymes present in brain homogenates than did compounds substituted in the 3,4- or 3,4,5-positions. Accordingly, 3,4,5-trimethyl-β-phenethylamine should provide a more reliable indication of the change in psychochemical activity brought about by replacement of methoxyl by methyl in the mescaline nucleus.

The key reaction in the synthesis of 3,4,5-trimethyl-β-phenethylamine was the isomerization of 2,4,6-trimethylacetophenone, readily obtained by Friedel-Crafts acetylation of mesitylene, to 3,4,5-trimethylacetophenone by heating with anhydrous aluminum chloride.[4] Transformation of the acetyl group to the β-aminoethyl side-chain was readily accomplished *via* the Kindler modification of the Willgerodt reaction. Conversion of the 3,4,5-trimethylphenylacetic acid so obtained to the corresponding amide, and reduction with lithium aluminum hydride, afforded the desired 3,4,5-trimethyl-β-phenethylamine. This route to β-phenethylamines is convenient when the corresponding acetophenones are available and is worthy of further exploitation.

Results of the physiological evaluation of 3,4,5-trimethyl-β-phenethylamine will be published elsewhere.

EXPERIMENTAL[5]

3,4,5-Trimethylphenylacetothiomorpholide. 2,4,6-Trimethylacetophenone, b.p. 109–111°/9 mm., was obtained in 88% yield by the action of acetic anhydride on mesitylene in the presence of anhydrous aluminum chloride in carbon disulfide solution.[6] Isomerization to 3,4,5-trimethylacetophenone was accomplished as described[4] by heating a mixture of 71 g. of 2,4,6-trimethylacetophenone with 116 g. of anhydrous aluminum chloride at 170° for 1.5 hr.; yield, 56.6 g. (80%) of a pale yellow oil, b.p. 135–140°/12 mm. A mixture of 48.6 g. of 3,4,5-trimethylacetophenone, 39 g. of redistilled morpholine, and 14.4 g. of sulfur was refluxed for 12 hr. The warm reaction mixture was poured into 175 ml. of hot ethanol and allowed to cool to permit the product to crystallize; yield, 62.6 g. (79%) of 3,4,5-trimethylphenylacetothiomorpholide, m.p. 120–122°, sufficiently pure for the next step. A sample recrystallized from ethanol melted at 123–124°.

Anal. Calcd. for $C_{15}H_{21}NOS$: N, 5.3; S, 12.2. Found: N, 5.2; S, 12.0.

3,4,5-Trimethylphenylacetic acid. A mixture of 51 g. of 3,4,5-trimethylphenylacetothiomorpholide, 110 ml. of acetic acid, 16 ml. of sulfuric acid, and 25 ml. of water was heated under reflux for 5 hr. and decanted from the small amount of tar formed into 850 ml. of water with stirring. The precipitated crude product was collected, washed with water, and heated with 225 ml. of 5% aqueous sodium hydroxide. Filtration from a small amount of insoluble matter and acidification with dilute hydrochloric acid gave 30 g. (88%) of 3,4,5-trimethylphenylacetic acid sufficiently pure for the next step. A sample recrystallized from benzene-petroleum ether melted at 125–126°.

Anal. Calcd. for $C_{11}H_{14}O_2$: C, 74.1; H, 7.8; Neutr. Equiv. 178. Found: C, 74.0; H, 7.9; Neutr. Equiv. 180.

3,4,5-Trimethylphenylacetamide. After the initial vigorous reaction had subsided, a mixture of 21.3 g. of 3,4,5-trimethylphenylacetic acid and 25 g. of phosphorus pentachloride was warmed on the steam bath for 10 min. The mixture was distilled under reduced pressure to remove phosphorus oxychloride, and the residue was added gradually to 100 ml. of ice-cooled concentrated aqueous ammonia. The precipitated amide was collected, washed with water, and air dried; recrystallization from benzene plus a small amount of ethanol afforded 18 g. (85%) of the pure amide, m.p. 183–184°.

Anal. Calcd. for $C_{11}H_{15}NO$: C, 74.6; H, 8.5; N, 7.9. Found: C, 74.4; H, 8.6; N, 7.9.

3,4,5-Trimethyl-β-phenethylamine. To a stirred suspension of 8.6 g. of lithium aluminum hydride in 500 ml. of absolute ether, was added a solution of 10 g. of 3,4,5-trimethylphenylacetamide in 600 ml. of boiling reagent benzene, using additional hot benzene to redissolve material which crystallized during the addition. The reaction mixture was stirred and refluxed for 22 hr. and then hydrolyzed by cautious addition of water and 10% sulfuric acid. A white solid insoluble in both the ether and aqueous layers was formed and collected by filtration. This material proved to be the insoluble sulfate of 3,4,5-trimethyl-β-phenethylamine contaminated with aluminum salts. Upon heating with concentrated hydrochloric acid, the crude product dissolved, and the hydrochloride of 3,4,5-trimethyl-β-phenethylamine crystallized in the form of colorless lustrous plates on cooling. The yield was 10.1 g. (89%), m.p. 249–250° after recrystallization from methanol-ethyl acetate.

Anal. Calcd. for $C_{11}H_{18}ClN$: Cl, 17.8; N, 7.0. Found: Cl, 17.7; N, 6.9.

The *benzoyl derivative* melted at 153–154°.

Anal. Calcd. for $C_{18}H_{21}NO$: C, 80.9; H, 7.9. Found: C, 80.6; H, 7.7.

BATTELLE MEMORIAL INSTITUTE
COLUMBUS 1, OHIO
FELS RESEARCH INSTITUTE
YELLOW SPRINGS, OHIO

(3) F. Benington, R. D. Morin, and L. C. Clark, Jr., *J. Org. Chem.*, **20**, 1292 (1955).

(4) G. Baddeley, *J. Chem. Soc.*, 232 (1944).

(5) Melting points are uncorrected.

(6) Shirley, *Preparation of Organic Intermediates*, John Wiley & Sons, Inc., New York, 1951, p. 190.

A Convenient Synthesis of *m*-Anisidine

PANKAJA K. KADABA AND SAMUEL P. MASSIE

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In studies on the preparation of ring derivatives of phenothiazines[1] beginning with the corresponding anilines, *m*-anisidine was required. This compound is not commercially available, in spite of its relative importance as a starting material, particularly in the synthesis and degradative studies of some indole alkaloids, notably harmine[2] and reserpine.[3] The conventional method of preparing *m*-

(1) S. P. Massie and P. K. Kadaba, *J. Org. Chem.*, **21**, 347 (1956).

(2) W. O. Kermack, W. H. Perkin, and R. Robinson, *J. Chem. Soc.*, **199**, 1641 (1921); E. Spath and E. Lederer, *Ber.*, **63**, 123 (1930).

(3) C. F. Huebner, H. B. McPhillany, A. F. St. Andre, and E. Schlitter, *J. Am. Chem. Soc.*, **77**, 473 (1955).

anisidine,[4] using *m*-nitroaniline as the starting material, is long and tedious, and involves diazotization, hydrolysis, methylation, and reduction. Its preparation by rearrangement of the product from *o*-chloroanisole with sodium amide in liquid ammonia is not very convenient.[5] A convenient method of making *m*-anisidine, starting with *m*-aminophenol, has been reported by Reverdin,[6] and involves acylation of the amino group, followed by methylation with dimethyl sulfate and subsequent hydrolysis. However, in spite of the apparent simplicity of this method it has not been widely used by other workers, and in recent studies on the constitution of tazettine,[7] as lycoris alkaloid, the above described conventional method for the synthesis of *m*-anisidine was used.

We wish to report here the details of a single step synthesis of *m*-anisidine by direct methylation of the easily available and inexpensive *m*-aminophenol using dimethyl sulfate, as well as the results of reinvestigation of the earlier procedure of Reverdin.[6] The use of methyl *p*-toluenesulfonate as a methylating agent was also successful but offered no advantage.

We acknowledge the financial support of the National Cancer Institute (Grant C-2450) and we thank them very much.

EXPERIMENTAL

m-Anisidine from m-Aminophenol. A mixture of *m*-aminophenol (25 g.), dimethyl sulfate, technical grade (50 g.), anhydrous potassium carbonate (100 g.), and potassium hydroxide (25 g.) was refluxed in anhydrous methyl ethyl ketone (500 ml.) for 120 hr. The cooled reaction mixture was poured into an excess of cold water and let stand overnight to decompose excess dimethyl sulfate. It was then extracted with ether and the ether extract dried and distilled to remove solvent. The oily residue was distilled under reduced pressure to give 25.5 g. (91%) of pale yellow *m*-anisidine, b.p. 81–86°/2 mm.

m-Anisidine from m-acetylaminophenol. A mixture of *m*-acetylaminophenol (43 g.), dimethyl sulfate, technical grade (50 g.) and anhydrous potassium carbonate (100 g.) was refluxed in anhydrous methyl ethyl ketone (500 ml.) for 48 hr. The mixture was then cooled, filtered, and the residual potassium carbonate washed with ether. The washings were combined with the filtrate and the solvents removed by distillation. The syrupy residue of *m*-acetaniside (a portion was crystallized from benzene petroleum ether to give colorless, shining crystals, m.p. 79–80°)[6] was hydrolyzed by refluxing with concentrated hydrochloric acid for 4 hr. The cooled mixture was made strongly alkaline with sodium hydroxide solution, and extracted with ether. Removal of the ether, subsequent to drying and distillation of the residue, gave 20 g. (57%) of pale yellow *m*-anisidine, distilling at 79° under 1 mm. pressure. The reaction time could be reduced to 6 hr., but the yield was lower.

m-Acetylaminophenol was methylated and hydrolyzed following the procedure of Reverdin. The yields were in order of 50–55% as against the 90% claimed by Reverdin.

DEPARTMENT OF CHEMISTRY
FISK UNIVERSITY
NASHVILLE 8, TENN.

(4) D. A. Shirley, *Preparation of Organic Intermediates*, John Wiley and Sons, New York, N. Y., 1951, p. 213.

(5) H. Gilman and R. H. Kyle, *J. Am. Chem. Soc.*, **74**, 3028 (1952).

(6) F. Reverdin and A. de Luc, *Ber.*, **47**, 1537 (1914).

(7) H. Kondo, T. Ikada, and J. Taga, *Ann. Rept. ITSUU Lab. Japan*, **3**, 659 (1952); [*Chem. Abstr.* **47**, 7417 (1953)].

Analogs of Hexaphenylethane. VI. Triphenylgermyltriphenyltin[1]

HENRY GILMAN AND CLARE W. GEROW

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There has been reported only one organic compound containing a germanium-tin bond. This was triphenylgermyltrimethyltin reported by Kraus and Foster.[2] We have prepared triphenylgermyltriphenyltin as a member of a series to compare the strengths of the bonds between various Group IV-B elements. The preparation was carried out by coupling triphenylgermylpotassium with triphenyltin chloride according to the equation

$$(C_6H_5)_3GeK + (C_6H_5)_3SnCl \rightarrow (C_6H_5)_3GeSn(C_6H_5)_3 + KCl$$

The mode of addition was found to be important in this reaction, for it was found that when the triphenyltin chloride was added to the triphenylgermylpotassium a 60% yield of triphenylgermyltriphenyltin was isolated; however, when the triphenylgermylpotassium was added to the triphenyltin chloride only a mixture of products was formed which could not be separated into its components. A mixture was also formed when triphenyltinlithium was allowed to react with triphenylchlorogermane, and when triphenylgermyllithium was allowed to react with triphenyltin chloride. It is believed that the mixtures obtained above contain hexaphenyldigermane, triphenylgermyltriphenyltin, and possibly hexaphenylditin. The presence of hexaphenyldigermane and probably triphenylgermyltriphenyltin was confirmed by treating the mixture obtained from the reaction of triphenylgermyllithium and triphenyltin chloride with iodine. Hexaphenyldigermane, which is unaffected by iodine, was isolated in 46% yield and triphenyliodogermane was found in 14% yield. The triphenyliodogermane probably arose from the cleavage of triphenylgermyltriphenyltin, and the nonisolation of a tin compound was probably due to the cleavage of more than one phenyl group from the tin atom.

The above mixtures could have been formed from a coupling of the many species present in the

(1) For paper V of this series see H. Gilman and C. W. Gerow, *J. Am. Chem. Soc.*, 78, 5823 (1956).

(2) C. A. Kraus and L. S. Foster, *J. Am. Chem. Soc.*, **49**, 457 (1927).

reaction mixture due to a halogen-metal interconversion reaction between the triphenylgermyllithium and the triphenyltin chloride or between the triphenyltinlithium and the triphenylchlorogermane. Similar halogen-metal interconversion reactions have been observed between triphenylgermylpotassium and triphenylchlorosilane,[1] between triphenylmethylsodium and triphenylbromosilane,[3] and between triphenylsilylpotassium and triphenylchloromethane.[3]

Triphenylgermyltriphenyltin is a white solid melting at 284–286°; when heated above its melting point it decomposes. It is stable to oxygen in chloroform at room temperature. However, it is partially decomposed in refluxing xylene either in the presence or absence of air. In the former respect it is similar to triphenylgermyltriphenylsilane,[1] hexaphenyldisilane,[4] and hexaphenyldigermane,[5] all of which are unaffected by oxygen. The Ge—Sn bond is readily cleaved by iodine and organolithium reagents. In these reactions triphenylgermyltriphenyltin is entirely different from hexaphenyldisilane,[4] hexaphenyldigermane,[5] and triphenylgermyltriphenylsilane,[1] all of which are unaffected by both iodine and organolithium reagents. When triphenylgermyltriphenyltin is allowed to react with phenyllithium a mixture of tetraphenylgermane and tetraphenyltin apparently is formed. With butyllithium there is isolated, subsequent to carbonation, triphenylgermanecarboxylic acid and hexaphenyldigermane; however, no pure tin compound was found.

Triphenylgermyltriphenyltin is not extensively affected by sodium-potassium alloy unless an initiator such as tetrahydrofuran is added, in which case cleavage proceeds easily. In this respect the Ge—Sn bond is like the Ge—Ge bond in hexaphenyldigermane[5] which is not affected by sodium-potassium alloy unless an initiator is added. The Ge—Si[1] and Si—Si[6] bonds in triphenylgermyltriphenylsilane and hexaphenyldisilane are readily cleaved under the same conditions.

EXPERIMENTAL[7]

Preparation of triphenylgermyltriphenyltin. To an ether suspension of triphenylgermylpotassium prepared by the cleavage of 19.1 g. (0.05 mole) of tetraphenylgermane with sodium-potassium alloy, according to recent directions[5] there was added an ether suspension of 19.3 g. (0.05 mole) of triphenyltin chloride. After stirring overnight the mixture was poured into a saturated ammonium chloride solution, and then was filtered to give a solid melting over the range 250–275° with some decomposition. This material was crystallized twice from benzene to give 19.5 g. (60%) of product melting at 284–286°.

Anal. Calcd. for $C_{36}H_{30}GeSn$: GeSn, 29.25. Found: GeSn, 29.28, 29.46.

Using the same procedure, two other runs gave 26 and 64% yields. When the triphenylgermylpotassium was added to the triphenyltin chloride there was obtained a mixture from which no pure product could be isolated. A mixture was likewise formed when triphenylchlorogermane was allowed to react with triphenyltinlithium and when triphenylgermyllithium was allowed to react with triphenyltin chloride.

Cleavage experiments with triphenylgermyltriphenyltin. With oxygen. When 1.0 g. of triphenylgermyltriphenyltin was dissolved in 50 ml. of chloroform and dry air was passed through it for 24 hr. there was recovered 0.95 g. of starting material melting at 284–287°. When refluxing xylene was substituted for chloroform there was recovered only 0.6 g. of pure starting material. However, it is believed that the loss of material was due to decomposition by heat because when 5.0 g. of triphenylgermyltriphenyltin was refluxed for 24 hr. in 25 ml. of xylene in a nitrogen atmosphere only 4.5 g. of impure starting material was recovered.

With iodine. When a chloroform solution of iodine was added to 5.0 g. of triphenylgermyltriphenyltin dissolved in 50 ml. of chloroform, the color was dispelled immediately after each small addition. The iodine was added as long as the color was discharged at room temperature, then the mixture was heated to boiling and the addition was continued until a large excess of iodine was present. The solvent was removed by distillation to leave a liquid residue which was washed with petroleum ether (b.p. 60–70°) to give a quantitative yield of triphenyliodogermane melting at 155–157°. No tin compound was isolated.

When 1.12 g. (0.0044 mole) of iodine dissolved in 50 ml. of chloroform was added dropwise to 2.9 g. (0.0044 mole) of triphenylgermyltriphenyltin dissolved in 70 ml. of chloroform, the color was discharged immediately after each small addition during the first few drops. After about half of the iodine had been added the color took longer to disappear, and at this point the solution was heated to boiling and the remainder of the iodine was added dropwise. When the addition was complete the color of the solution was yellow. The chloroform was removed by distillation and the residue was washed with petroleum ether (b.p. 60–70°) to give 0.8 g. of insoluble solid melting over the range 260–275°. This material was washed with ether to give 0.6 g. of recovered starting material melting at 283–285°. The petroleum ether filtrate from above was cooled and there crystallized 2.05 g. of solid melting over the range 110–116°. Repeated crystallization of this material from petroleum ether (b.p. 60–70°) gave no pure product. It is believed that a mixture of triphenyliodogermane and triphenyltin iodide was present. An infrared spectrum of this mixture showed absorption peaks at 1090 $cm.^{-1}$ and 1070 $cm.^{-1}$, indicative of the phenylgermanium and phenyl-tin bonds.

With sodium-potassium alloy. The cleavage experiments with triphenylgermyltriphenyltin and sodium-potassium alloy were not clean-cut. Several cleavage experiments, however, indicate that reaction is not extensive. When 3.3 g. (0.005 mole) of triphenylgermyltriphenyltin was stirred 71 hr. with 0.6 ml. (0.012 g. atom of potassium) of sodium-potassium alloy in a small amount of ether there was recovered 2.5 g. (70%) of impure starting material melting over the range 260–295°. However, when the same amount of triphenylgermyltriphenyltin was stirred 70 hr. under the same conditions, except that 20 drops of tetrahydrofuran was added, the addition of propyl bromide to derivatize the products led to the isolation of 0.4 g. (26%) of hexaphenyldigermane and 1.6 g. of what is believed to be a mixture of triphenyl-*n*-propylgermane and triphenyl-*n*-propyltin melt-

(3) A. G. Brook, H. Gilman, and L. S. Miller, *J. Am. Chem. Soc.*, 75, 4759 (1953).

(4) W. Schlenk, J. Renning, and G. Rackey, *Ber.*, 44, 1178 (1911).

(5) H. Gilman and C. W. Gerow, *J. Am. Chem. Soc.*, 77, 5509 (1955).

(6) H. Gilman and T. C. Wu, *J. Am. Chem. Soc.*, 73, 4031 (1951).

(7) All melting points are uncorrected. Reactions involving reactive organometallic compounds were carried out in an atmosphere of dry, oxygen-free nitrogen.

ing over the range 77–82°. Repeated crystallization of this material from methanol gave no pure products. An infrared spectrum of this mixture showed absorption peaks at 1090 cm.$^{-1}$ and 1070 cm.$^{-1}$, which a large number of spectra have shown to be indicative of the phenyl-germanium and phenyl-tin bonds. The melting point of the mixture is consistent with what one might expect from a mixture of triphenyl-*n*-propylgermane and triphenyl-*n*-propyltin.

With phenyllithium. To an ether solution of phenyllithium prepared from 7.85 g. (0.05 mole) of bromobenzene there was added 3.27 g. (0.005 mole) of triphenylgermyltriphenyltin. After stirring overnight the mixture was hydrolyzed by the addition of water. Filtration then gave 3.52 g. of solid melting over the range 217–223°. From the ether layer there was obtained an additional 0.65 g. of solid melting over the range 222–226°. Repeated crystallization of these materials from benzene gave no pure products. It is believed a mixture of tetraphenylgermane and tetraphenyltin is present. The infrared spectrum of this mixture also showed absorption peaks at 1090 cm.$^{-1}$ and 1070 cm.$^{-1}$ indicative of the phenyl-germanium and phenyl-tin bonds. The melting point of the mixture is consistent with the melting point that Drew and Landquist[8] found for a mixture of tetraphenylgermane and tetraphenyltin in their studies on mixture melting points of the tetraphenyls of the Group IV-B elements; they reported a melting point of 223–224° for their synthetic mixture.

With butyllithium. To a suspension of 3.27 g. (0.005 mole) of triphenylgermyltriphenyltin in 20 ml. of ether there was added rapidly 10 ml. of a 0.1*N* solution of *n*-butyllithium. After stirring 24 hr. Color Test I[9] was positive and Color Test II[10] was negative. The mixture was then carbonated by pouring it into an ether–Dry-Ice slurry, and after warming to room temperature water was added and the alkaline layer was separated. The ether layer was extracted twice with 50 ml.-portions of 5% sodium hydroxide solution, and then the combined alkaline layers were acidified by the addition of concentrated hydrochloric acid. There precipitated a solid weighing 0.6 g. which was recrystallized from ethanol to give 0.16 g. (9%) of triphenylgermanecarboxylic acid melting at 186° with the evolution of carbon monoxide. The ether layer above was filtered to give 0.75 g. of solid melting over the range 300–320°. Recrystallization of this material from benzene gave 0.35 g. of hexaphenyldigermane melting at 338–340°. The ether solution was dried over anhydrous sodium sulfate and the solvent was removed by distillation to leave a residue which was washed with methanol to give 0.4 g. of material melting over the range 210–230°. Recrystallization of this material gave no pure products.

Acknowledgment. The authors wish to express their appreciation to the Materials Laboratory, Wright Air Development Center, Wright-Patterson Air Force Base, Ohio, for their financial support of this work. They are also grateful to the Institute for Atomic Research, Iowa State College, Ames, Iowa, for assistance in the infrared determinations.

Department of Chemistry
Iowa State College
Ames, Iowa

(8) H. D. K. Drew and J. K. Landquist, *J. Chem. Soc.*, 1480 (1935).

(9) H. Gilman and F. Schultz, *J. Am. Chem. Soc.*, **47**, 2002 (1925).

(10) H. Gilman and J. Swiss, *J. Am. Chem. Soc.*, 62, 1847 (1940).

Synthesis of Some Derivatives of Phenothiasilin, A Silicon Analog of Thiaxanthene

Katashi Oita and Henry Gilman

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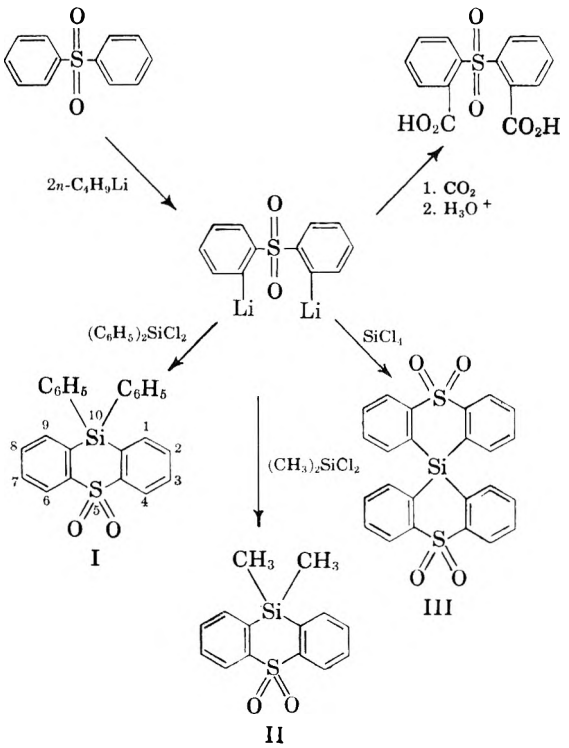
In view of the success attained in the preparation of several derivatives of phenoxasilin,[1] a silicon analog of xanthene, the synthesis of a new heterocyclic system in which silicon and sulfur were present as hetero atoms was undertaken. The compounds prepared were 10,10-diphenylphenothiasilin-5,5-dioxide (I) and 10,10-dimethylphenothiasilin-5,5-dioxide[2] (II), silicon analogs of 10,10-diphenylthiaxanthene-5,5-dioxide and 10,10-dimethylthiaxanthene-5,5-dioxide, respectively. A Fisher-Hirschfelder-Taylor model of phenothiasilin-5,5-dioxide indicated very little strain.

These phenothiasilin derivatives were prepared from the reaction of 2,2′-dilithiodiphenyl sulfone with the corresponding dichlorosilane. The dimetalation of diphenyl sulfone was carried out in accordance with the previously reported low-temperature procedure.[3] The identity of 2,2′-dilithiodiphenyl sulfone has been confirmed by its conversion to 2,2′-dicarboxydiphenyl sulfone.[3]



As in the syntheses of phenoxasilin derivatives[1]

(1) K. Oita and H. Gilman, *J. Am. Chem. Soc.*, 79, 339 (1957).

(2) The names and the numbering system used herein were recommended by the editorial staff of the *Chemical Abstracts*.

(3) H. Gilman and D. L. Esmay, *J. Am. Chem. Soc.*, **75**, 278 (1953).

the optimum yields are obtained if the reaction of the dilithium intermediate and the dichlorosilane is carried out under the conditions that would keep the concentration of either one or both of the reactants in the reaction mixture low. The method of simultaneous addition of the two reactants to a vigorously stirred, refluxing, reaction mixture[1] was not used with 2,2′-dilithiodiphenyl sulfone because it is stable only at a relatively low temperature. Therefore, the dichlorosilane solution was slowly added to a cooled (0° or less), extremely dilute, ethereal suspension of 2,2′-dilithiodiphenyl sulfone, and this temperature was maintained until most of the reaction had occurred. Chromatographic separation was employed to remove silanols or silanediols formed upon the hydrolysis of the unreacted or partially reacted diphenyl- and dimethyldichlorosilane.

The structure of 10,10-diphenylphenothiasilin-5,5-dioxide was supported by its infrared spectrum which showed aromatic-substitution bands at 13.1 and 13.5 μ, characteristic of an *ortho*-disubstituted benzene and a monosubstituted benzene, respectively.

An attempt was made to prepare 10,10′-spirobiphenothiasilin-5,5,5′,5′-tetroxide (III) from the reaction of two equivalents of 2,2′-dilithiodiphenyl sulfone and one of silicon tetrachloride. The desired product has not been isolated as yet.

EXPERIMENTAL[4]

10,10-Diphenylphenothiasilin-5,5-dioxide (I). To a well stirred, ethereal suspension (1156 ml.) containing 0.1 mole of 2,2′-dilithiodiphenyl sulfone prepared in accordance with the published procedure[3] was added over a period of 70 min. a solution of 25.3 g. (0.1 mole) of diphenyldichlorosilane in 100 ml. of ether. The reaction mixture was maintained at 0° during the addition and then at an ether-reflux temperature for 12 hr. The chocolate-brown suspension was hydrolyzed with 200 ml. of water, stirred, and filtered. The ethereal layer of the filtrate was separated, dried over anhydrous sodium sulfate, and chromatographed on activated alumina with ether as an eluant. The sticky paste obtained on removing the ether from the eluate was digested with petroleum ether (b.p. 77–115°), cooled, and filtered. The resulting white solid was recrystallized once from a mixture of petroleum ether (b.p. 77–115°), once from ethyl acetate, and twice from a mixture of petroleum ether (b.p. 77–115°) and benzene to yield 3.34 g. (8.4%) of 10,10-diphenylphenothiasilin-5,5-dioxide melting at 208–209°. The analytical sample obtained by another recrystallization from a mixture of petroleum ether (b.p. 77–115°) and benzene melted at 208.5–209°.

Anal. Calcd. for $C_{24}H_{18}O_2SSi$: S, 8.05; Si, 7.05. Found: S, 8.10, 7.94; Si, 7.06, 7.20.

The infrared spectrum measured in a carbon disulfide solution had sulfone bands at 7.6 and 8.6 μ, an *ortho* disubstituted benzene band at 13.1 μ, and a monosubstituted benzene band at 13.5 μ.

The analytical sample melted at 208.5–209° to form a clear, colorless melt and volatilized[5] at 450° with some decomposition. At 490° the decomposition appeared to be complete.

10,10-Dimethylphenothiasilin-5,5-dioxide (II). To a yellow suspension of 2,2′-dilithiodiphenyl sulfone prepared from 12.6 g. (0.058 mole) of diphenyl sulfone in 580 ml. of ether and 0.116 mole of *n*-butyllithium (1.21*M* ethereal solution) was added over a period of 90 min. a solution of 7.34 g. (0.058 mole) of dimethyldichlorosilane in 50 ml. of ether. During the addition period the temperature of the reaction mixture was maintained at −20°. After stirring at approximately 0° overnight Color Test I[6] was still positive; therefore, it was stirred at room temperature for 8 hr. The reaction mixture which now gave a negative Color Test I was hydrolyzed with 150 ml. of water, stirred, filtered, and the ethereal phase was separated. This ethereal solution was dried over anhydrous sodium sulfate and chromatographed on activated alumina using ether as an eluant. The eluate upon removing the solvent yielded 12.4 g. of a white material melting over the range 78–150°. Successive recrystallizations from ethanol and from a mixture of ethanol and petroleum ether (b.p. 77–115°) gave 8.12 g. of white plates melting over the range 103–140°. When this product was recrystallized from excess ethanol, there was obtained 3.81 g. (24%) of 10,10-dimethylphenothiasilin-5,5-dioxide (m.p. 160.5–161.5°) in a form of square, platelike crystals.

Anal. Calcd. for $C_{14}H_{14}O_2SSi$: C, 61.2; H, 5.15. Found: C, 61.1, 61.2; H, 5.30, 5.11.

The infrared spectrum determined in a carbon disulfide solution and the assigned structure were compatible.

This compound upon melting formed a clear, colorless liquid which volatilized completely without decomposition at 400°. At 420° refluxing of the condensate in the capillary tube occurred but no discoloration was observed.

Attempted preparation of 10,10′-spirobiphenothiasilin-5,5,-5′,5′-tetroxide (III). The crude product from the reaction of 0.1 mole of 2,2′-dilithiodiphenyl sulfone and 0.05 mole of silicon tetrachloride was extracted with methyl ethyl ketone in a Soxhlet extraction apparatus. The extract was concentrated and the solid obtained was digested with petroleum ether (b.p. 60–70°), filtered and air-dried to yield 6.35 g. of a white powder melting over the range 230–290° with decomposition. This material was insoluble in benzene, xylene, petroleum ether (b.p. 77–115°), ethylene glycol dimethyl ether, chloroform, carbon tetrachloride, ethanol, dioxane, and glacial acetic acid. Recrystallization from a mixture of methyl ethyl ketone and petroleum ether (b.p. 77–115°) has not resulted yet in any significant amount of purification.

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AMES, IOWA

(4) All melting points reported are uncorrected and all reactions were carried out under an atmosphere of dry, oxygen-free nitrogen.

(5) Volatility was determined by inserting a melting point capillary containing a small amount of a sample into a copper block which was heated with a Bunsen flame. The volatilization temperature was arbitrarily taken as the temperature at which approximately one-eighth of an inch of condensate appeared in the capillary tube above the block.

(6) H. Gilman and F. Schulze, *J. Am. Chem. Soc.* **47**, 2002 (1925).

Cleavage Studies in the Carbazole and Phenothiazine Systems

HENRY GILMAN, JULIAN B. HONEYCUTT, JR., AND ROBERT K. INGHAM

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In connection with general studies of carbazole and phenothiazine derivatives, methods were sought for determining the position taken by the entering substituent in various substitution reactions. The reports on the lithium[1] and Raney nickel[2] cleavage of dibenzofuran and dibenzothiophene, and those on the action of Raney nickel on phenothiazine[3] and 2-phenothiazinecarboxylic acid[4] prompted us to extend the cleavage studies to carbazole, phenothiazine, and their N-ethyl derivatives. Copper, which has been used to convert phenothiazine to carbazole,[5,6] and Raney nickel have not as yet been reacted with 9-ethylcarbazole or 10-ethylphenothiazine.

The reaction between metallic lithium and phenothiazine in refluxing dioxane followed by hydrolysis yielded *o*-mercaptodiphenylamine and diphenylamine. Termination of the reaction by carbonation gave only *o*-mercaptodiphenylamine. When the reaction was carried out in anhydrous ether, the only material isolated was phenothiazine. 10-Ethylphenothiazine and lithium in refluxing dioxane yielded a yellow-brown oil which was assumed to be *o*-mercaptodiphenylethylamine. In contrast to the phenothiazine system, neither carbazole nor 9-ethylcarbazole underwent cleavage. Earlier Signaigo[7] found that phenothiazine in dioxane with hydrogen and a cobalt sulfide catalyst at elevated temperature and pressure gave diphenylamine and *o*-mercaptodiphenylamine. These are the same products which we obtained using lithium metal.

The results obtained indicate that under the conditions employed the carbon-nitrogen bonds within the carbazole and phenothiazine systems are not cleaved. That this inertness is not due to any influence of the sulfur atom is shown by the almost complete recovery of starting material when carbazole or 9-ethylcarbazole is used as a reactant. It would be interesting to determine the extent of cleavage with phenoxazine and, particularly, 5,10-dihydrophenazine.

The isolation of both *o*-mercaptodiphenylamine and diphenylamine from the reaction with phenothiazine can be explained by the mechanism previously proposed[1] which involves cleavage of one or both carbon-sulfur bonds to give carbon-lithium bonds. The failure to obtain a positive Color Test I[8] and to isolate any carboxylic acid on carbonation leads to the conclusion that any intermediate organometallic compound is immediately destroyed by the refluxing dioxane.

The possible use of refluxing hydriodic acid, successfully employed in determining the position of metalation of 10-ethyl- and 10-phenylphenothiazine,[9] appeared to warrant investigation as a cleavage reagent. As with lithium, 9-ethylcarbazole was unaffected by the reagent while 10-ethylphenothiazine yielded mainly the parent heterocycle, phenothiazine. Although a portion of the phenothiazine derivative was desulfurized, as evidenced by the odor of H_2S, the isolation of such a substantial amount of phenothiazine is in marked contrast to the results reported previously; it was found that the 10-ethyl- and 10-phenylphenothiazinecarboxylic acids formed by metalation and carbonation decomposed to give *m*-carboxydiphenylamine and *m*-carboxytriphenylamine, respectively.[9] Thus, desulfurization occurred with both carboxylic acids, but only the N-ethyl group was removed. The desulfurization probably involves the carboxyl group, but additional information must be obtained before the mechanism can be elucidated.

EXPERIMENTAL[10]

Lithium cleavage of phenothiazine. Run I. To 200 ml. of purified dioxane[11] under a nitrogen atmosphere in a three-necked flask equipped with a condenser and mechanical stirrer were added 19.9 g. (0.1 mole) of phenothiazine and 2.22 g. (0.32 g. atom) of lithium. The mixture was stirred and heated to reflux temperature and there maintained for 15 hr. The odor of hydrogen sulfide was evident and a lead acetate test for this substance was positive soon after heating was begun. Color Test I,[8] taken intermittently during the reaction, was negative. After 15 hr. the reaction mixture was cooled and slowly hydrolyzed with a water-dioxane solution. The solvent was distilled off at reduced pressure leaving a light brown, gummy solid. The residue was extracted with two 50 ml. portions of 5% sodium hydroxide, washed with water, extracted with two 50 ml. portions of 5% hydrochloric acid, and then with two 25 ml. portions of methanol. Two recrystallizations from toluene of the residual material gave 7.2 g. (36% recovery) of phenothiazine; a mixed melting point was not depressed. Neutralization of the alkaline extract gave a yellow-brown oil with a mercaptan odor. The oil was dissolved in ether. Ex-

(1) H. Gilman and D. L. Esmay, *J. Am. Chem. Soc.* **75**, 2947 (1953).

(2) F. F. Blicke and D. G. Sheets, *J. Am. Chem. Soc.* **70**, 3768 (1948).

(3) K. H. Shah, B. D. Tilak, and K. Venkataraman, *Proc. Indian Acad. Sci.*, 28A, 142 (1948) [*C. A.*, 44, 3958 (1950)].

(4) R. Baltzly, M. Harfenist, and F. J. Webb, *J. Am. Chem. Soc.*, 68, 2673 (1946).

(5) A. Goske, *Ber.*, **20**, 232 (1887).

(6) P. Charpentier, *Compt. rend.*, **225**, 306 (1947).

(7) F. K. Signaigo, U. S. Patent 2,402,686 [*Chem. Abstr.*, 40, 5767 (1946)].

(8) H. Gilman and F. Schulze, *J. Am. Chem. Soc.*, **47**, 2002 (1925).

(9) H. Gilman, P. R. Van Ess, and D. A. Shirley, *J. Am. Chem. Soc.*, 66, 1214 (1944).

(10) All melting points are uncorrected.

(11) L. F. Fieser, *Experiments in Organic Chemistry*, D. C. Heath and Co., New York, N. Y., 1941, p. 368.

traction of the ethereal solution with 5% sodium hydroxide and careful neutralization of the extract of 0–5° gave 5.8 g. (29%) of a yellow solid, melting at 35–37°. The solid changed to an oil again on standing, probably due to some oxidation to the disulfide. The mercaptan was dissolved in dilute sodium hydroxide and treated with an alcoholic solution of iodine until coloration due to iodine was evident. Filtration gave the disulfide of *o*-mercaptodiphenylamine; m.p. 161–162° (lit.,[12] 162°).

Anal. Calcd. for $C_{24}H_{20}N_2S_2$: S, 16.02. Found: S, 15.92, 15.81.

Neutralization of the hydrochloric acid extract gave no insoluble material.

Water dilution of the methanolic extract gave a light yellow solid which melted from 45–50°. Recrystallization from dilute ethanol gave 0.74 g. (4.4%) of diphenylamine melting at 51–52°; a mixed melting point with an authentic specimen showed no depression.

Run II. Run I was repeated, except that the reaction mixture was carbonated rather than hydrolyzed. Following the evaporation of the carbon dioxide the residue was extracted with sodium bicarbonate solution, then with dilute sodium hydroxide. No acid was obtained from the bicarbonate solution. Neutralization of the sodium hydroxide extract gave 6.7 g. (33.5%) of *o*-mercaptodiphenylamine, melting at 35–37°C; a mixed melting point with a sample from Run I was not depressed. No diphenylamine was isolated, but a 37.2% recovery of phenothiazine was obtained.

Run III. Run I was repeated employing anhydrous ether as a solvent rather than dioxane. The only material isolated was 16.0 g. (80.5% recovery) of phenothiazine.

Lithium cleavage of 10-ethylphenothiazine. Run I. 10-Ethylphenothiazine (11.2 g., 0.05 mole) and 0.8 g. (0.115 g. atom) of lithium were refluxed with 100 ml. of purified dioxane for 15 hr. as described above. Color Test I[8] was negative throughout the reaction. The reaction mixture was cooled and carbonated. The resulting mixture was acidified with 5% hydrochloric acid and the layers separated. The ether layer was extracted with an 8% sodium bicarbonate solution. Careful acidification of the cooled extract gave no solid product. The ethereal solution was then extracted with 10% sodium hydroxide solution. Neutralization gave 2.7 g. of a yellow-brown oil (24% if the product was *o*-mercaptodiphenylethylamine). Attempts to prepare the disulfide yielded a tan, gummy material which defied purification. The residual ether solution was evaporated and the residue recrystallized thrice from ethanol to give 3.5 g. (30.7% recovery) of 10-ethylphenothiazine; m.p. and mixed m.p. 100–102°. Neutralization of the original hydrochloric acid layer gave no precipitate.

Run II. Run I was repeated using 0.23 g. atom of lithium rather than 0.115 g. atom. A 33% yield of the mercaptan and a 28.6% recovery of 10-ethylphenothiazine were obtained. Again no diphenylethylamine was obtained.

Attempted lithium cleavage of carbazole. Run I. A mixture of 16.7 g. (0.1 mole) of carbazole and 4.0 g. (0.57 g. atom) of lithium in 200 ml. of purified dioxane was stirred and refluxed for 24 hr. The mixture was cooled and then poured over cracked ice. The resulting white solid (15.5 g., 93% recovery) was found to be carbazole; m.p. 239–243°. A mixed melting point determination with an authentic sample showed no depression.

Run II. Run I was repeated except that only 0.32 g. atom of lithium was employed and that the reaction mixture was carbonated instead of being hydrolyzed. Intermittent Color Test I[8] was negative. The reaction mixture was worked up as described above for the reaction with 10-ethylphenothiazine. The only product isolated was carbazole (88% recovery); m.p. and mixed m.p. 239–242°.

Attempted lithium cleavage of 9-ethylcarbazole. Run I. 9-Ethylcarbazole (19.5 g., 0.1 mole) and 2.0 g. (0.29 g. atom) of lithium were refluxed with 200 ml. of purified dioxane for 14 hr. The mixture was filtered through a glass wool plug into another flask and carefully hydrolyzed with a 1:1 water-dioxane solution. The addition of more water precipitated 16.0 g. (82% recovery) of 9-ethylcarbazole, melting at 63–66°. A mixed melting point determination with an authentic sample showed no depression.

Run II. Run I was repeated using 3.2 g. (0.46 g. atom) of lithium and a reflux time of 24 hr. Hydrolysis of the cooled reaction mixture gave a 95% recovery of 9-ethylcarbazole; m.p. and mixed m.p. 69–70°.

Run III. Run II was repeated except that the reaction mixture was carbonated instead of being hydrolyzed. The only product was 19.0 g. (97% recovery) of 9-ethylcarbazole; m.p. and mixed m.p. 69–70°.

Hydriodic acid cleavage of 10-ethylphenothiazine. To 11.35 g. (0.05 mole) of 10-ethylphenothiazine was added 50 ml. (0.275 mole) of 47% hydriodic acid. The mixture was heated to a moderate reflux and there maintained for 72 hr. with occasional shaking. The odor of hydrogen sulfide was evident throughout the reaction. After cooling, the yellowish solid was filtered off. Recrystallization from dilute ethanol gave 8.5 g. (85.9%) of phenothiazine; m.p. and mixed m.p. 186–187.5°. The original filtrate was extracted with ether and the extract evaporated to give only a very small amount of dark tar. The residual aqueous layer was made alkaline with sodium hydroxide to give 0.2 g. of white solid which did not melt at temperatures up to 365°. The material was insoluble in acetone, but soluble in cold 6*N* hydrochloric acid.

Attempted hydriodic acid cleavage of 9-ethylcarbazole. A mixture of 9.75 g. (0.05 mole) of 9-ethylcarbazole and 50 ml. (0.275 mole) of 47% hydriodic acid was refluxed gently for 72 hr. The only product isolated was 9.7 g. (99% recovery) of 9-ethylcarbazole; m.p. and mixed m.p. 68–70°.

A second experiment gave almost identical results.

CHEMICAL LABORATORY
IOWA STATE COLLEGE
AMES, IOWA

(12) A. I. Kiprianov and I. K. Ushenko, *J. Gen. Chem. (U.S.S.R.)*, **17**, 2201 (1947) [*Chem. Abstr.*, **42**, 5016 (1948)].

Thermal Rearrangement of Benzoylmeconic Acid

L. L. WOODS

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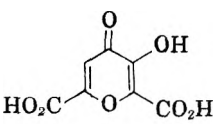
The chemistry of meconic acid, 3-hydroxy-4-pyrone-2,6-dicarboxylic acid (I), is very obscure and no reactions are recorded in which nuclear substitution of the compound has been effected.

There are reports, however, of the nuclear substitution of its partially decarboxylated derivative, comenic acid. Verkade[1] has described the partial decarboxylation of meconic acid with hydrochloric acid and has proven that the carboxyl lost during the reaction is from the position adjacent to the hydroxyl since the resulting comenic acid reacts with diazobenzene acetate. This indicates the presence in the compound of a methylene group which could only be located in the 2 position. The bromination of meconic acid also results

(1) P. E. Verkade, *Rec. trav. chim.*, **43**, 879 (1924).

in partial decarboxylation with the bromine taking the position vacated by the lost carboxyl.[2]



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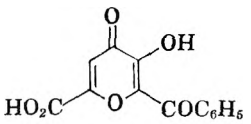


II

The experiments recorded in this report furnish proof that acylation of the pyrone ring can be accomplished from the phenolic ester of meconic acid by thermal rearrangement in which the acyl radical probably takes the position vacated by the carboxyl under the forcing conditions described. The 2-benzoylcomenic acid (II) thus formed is phenolic as indicated by the reaction with ferric chloride, and its ketonic nature is proved by the reaction with 2,4-dinitrophenylhydrazine. The fact that the bis-phenacyl ether ester derivative could be formed from the pyrone acid is additional proof of the postulated structure.

3-Benzoxychelidonic acid (benzoylmeconic acid) has been prepared to ascertain the properties of the substance before decarboxylation and rearrangement.

Confirmatory evidence that the disruptive forces of partial decarboxylation are responsible for the rearrangement is found in the fact that 3-benzoxycomenic acid from comenic acid, when heated at the same temperature over the same time interval, failed to produce the rearrangement.

An examination of the infrared spectrum shows most of the absorption peaks to be in about the expected positions. Only in the case of carbonyl and carboxyl absorption were unexpected values given. The presence of three different kinds of carbonyls, namely, carboxyl, pyrone, and benzoyl, greatly influence the absorption of each other. As a consequence the band with a peak at 1685 cm.$^{-1}$ broadens out to overlap 1725 cm.$^{-1}$ which is the carboxyl absorbing area exhibited by meconic acid.

EXPERIMENTAL[3]

2-Benzoylcomenic acid [II]. Twenty grams of meconic acid and 15 ml. benzoyl chloride were mixed in a 500 ml. flask which was fitted with an air cooled condenser to which was attached a gas trap. The mixture was heated at 145° for 24 hr. in a Fisher High-Temp oil bath. At the end of the reaction period 100 ml. of water was added and the white solid was filtered off. The yield was quantitative. The analytical sample was recrystallized 3 times from absolute ethanol.

The sample thus purified was placed in a vacuum sublimator and any sublimate collected at 130° or below was discarded. The residue was removed from the sublimator and again recrystallized from ethanol. The melting point was determined by the capillary tube method using Dow Corning 550 silicone oil. The compound rapidly discolored above 270° and was completely decomposed at 284°.

A sample of the purified substance gave a red-purple color with a 1 percent solution of ferric chloride.

Anal. Calcd. for $C_{13}H_8O_6$: C, 60.00; H, 3.09. Found: C, 60.38; H, 2.89.

Infrared data. The infrared spectrum was observed with a Perkin-Elmer Infrared Spectrophotometer Model 21 on a Nujol mull/capillary. Two peaks were observed for hydroxyl absorption at 3530 and 3380 cm.$^{-1}$ Other absorption bands observed were C=O at 1685, —C=C— 1642, and benzenoid ring at 1500 cm.$^{-1}$

The 2,4-dinitrophenylhydrazone of II was prepared by permitting 1 g. of II, 1 g. of 2,4-dinitrophenylhydrazine and 20 drops of concentrated hydrochloric acid to reflux for 5 min. with 50 ml. absolute ethanol. The mixture was filtered while hot into 50 ml. of water. A chocolate colored precipitate was obtained which was recrystallized once from absolute ethanol, m.p. 189–194° (dec.).

Anal. Calcd. for $C_{19}H_{12}N_4O_9$: N, 11.33. Found: N, 11.52.

Clemmensen reduction. Five grams of II was refluxed with 100 ml. of 6*N* hydrochloric acid and 20 g. of amalgamated zinc for 6 hr. The mixture was then filtered while hot and allowed to cool. Nearly 4 g. of crystals was obtained. The analytical sample was obtained by fractional sublimation of the material. The first half of the sample obtained by vacuum sublimation was discarded. The residue was then completely sublimed to a white compound, m.p. 119–121°.

An alcoholic solution of the compound gave a purple coloration with a dilute solution of ferric chloride.

Anal. Calcd. for $C_{14}H_{10}O_5$: C, 63.41; H, 4.09. Found: C, 63.19; H, 4.32.

3-Benzoxychelidonic acid. Three grams of meconic acid and 5 ml. benzoyl chloride were refluxed for 2 hr. in 100 ml. of dry benzene.

During the reaction a white insoluble powder was formed which, after the benzene solution had cooled, was filtered off. Recrystallizing the powder from ethanol produced hard chalky white rosettes which appeared to soften above 245°. As the temperature was raised above 260° there developed yellow spots which had decomposed at 269° to brown or black. This compound had no effect upon ferric chloride solutions.

Anal. Calcd. for $C_{14}H_8O_8$: C, 55.27; H, 2.65. Found: C, 55.01; H, 2.49.

Bis-phenacyl derivative. Two grams of II, 1 g. of sodium bicarbonate and 5 ml. of water were allowed to react. To this mixture was then added 2 g. of phenacyl bromide and 90 ml. absolute ethanol. After refluxing the material for 2 hr., it was made just acid with concentrated hydrochloric acid and filtered while hot. Storage in the refrigerator permitted pale yellow needles to separate. Recrystallization of the precipitate from absolute ethanol gave colorless needles, m.p. 119–121°.

Anal. Calcd. for $C_{29}H_{20}O_8$: C, 70.15; H, 4.06. Found: C, 70.02; H, 4.19.

3-Benzoxy comenic acid. Two g. of commercial meconic acid was heated in an open flask overnight at 155° immersed in a Fisher High-Temp oil bath. The resulting chalky white comenic acid was analyzed without further processing.

Anal. Calcd. for $C_6H_4O_5$: C, 46.12; H, 2.58. Found: C, 46.30; H, 2.69.

The comenic acid produced above, with the exception of the few milligrams removed for analysis, was treated with 3 g. of benzoyl chloride and the mixture was heated at 145° for 24 hr. The resulting product was a black viscous mass. The material was very soluble in alcohol and benzene. The compound was taken up in boiling heptane from which white curds precipitated on chilling. The air dried material consisted of white microscopic prisms, m.p. 112–114°.

Anal. Calcd. for $C_{13}H_8O_6$: C, 60.00; H, 3.09. Found: C, 59.79; H, 3.21.

(2) *Beilstein's Handbuch der organischen Chemie*, 4th Ed., Vol. 18, p. 503.

(3) All analyses were performed by Dr. Carl Tiedcke, Teaneck, N. J., and all melting points were determined on a Fisher-Johns melting point assembly, unless indicated otherwise.

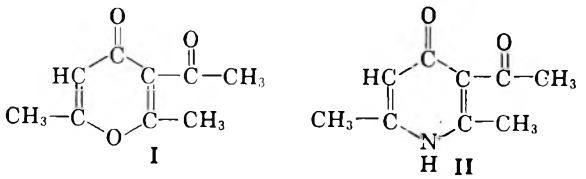
Acknowledgment. The author acknowledges with gratitude the assistance given by Dr. J. D. Edwards of the Veteran's Administration Hospital, Houston, Tex., and the Perkin Elmer Corp. for preparing infrared spectrograms. The author wishes to thank the Research Corp. for the financial support without which this study would not have been possible.

DEPARTMENT OF CHEMISTRY
TEXAS SOUTHERN UNIVERSITY
HOUSTON 4, TEX.

Some Reactions of 2,6-Dimethyl-4-pyrone

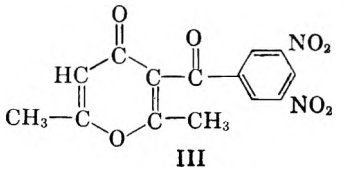
L. L. WOODS

Received August 31, 1956



I

II



III

A continuing study of the fundamental chemistry of 4-pyrones has led to an examination of the reactivity of 2,6-dimethyl-4-pyrone, which offers the signal advantage of being easily prepared from dehydroacetic acid,[1] but is a pyrone of considerable stability with both of the reactive 2- and 6-positions filled.

Numerous experiments have been attempted to ascertain with what reagents the compound would react and the first of these was found to be mercuric chloride. Since the mercurated pyrone was found to retain its mercury very tenaciously other avenues of nuclear substitution were sought.

The hydroxylation method of Tickle[2] was reviewed with the idea that an improvement of the procedure might offer a means of procuring enough 2,6-dimethyl-3-hydroxy-4-pyrone to serve as source material for further experimentation. However, in the author's hands so little of the compound was obtained that the reactions reported could not be confirmed. Modification of this experiment produced a pyrone-peroxide whose structure has not, as yet, been established. However, the fact that the pyrone undergoes direct mercuration indicates the presence of at least a measure of aromatic character.

In attempts to uncover other aromatic substitutions, a considerable number of methods of acylation were attempted using fuming stannic chloride, polyphosphoric acid, boron trifluoride etherate, and hydroiodic acid as catalysts. All were failures. The Crafts reaction with acetic anhydride was found, however, to effect acetylation in low yield.

2,6-Dimethyl-3-acetyl-4-pyrone (I) has a melting point very near that of 2,6-dimethyl-4-pyrone and cannot be separated from it by solvents; only fractional vacuum sublimation gave reasonable results. The preparation of the lutidone (II) and its 2,4-dinitrophenylhydrazone confirms the structure of I.

Since the previously described experiments have shown that acylation can be accomplished on the pyrone, many methods were tried in an attempt to improve yields and produce a crude compound of relatively high purity. The use of fused zinc chloride as a catalyst at the elevated temperatures furnished by refluxing xylene as a solvent makes possible the easy accomplishment of both objectives as described in the preparation of 2,6-dimethyl-3-(3,5-dinitrobenzoyl)-4-pyrone (III).

EXPERIMENTAL[3]

Mercuration of 2,6-dimethyl-4-pyrone. A mixture of 6.2 g. of 2,6-dimethyl-4-pyrone, 27.1 g. of mercuric chloride and 50 ml. of absolute ethanol was heated under reflux until all the reactants had gone into solution. The mixture was thoroughly chilled and the precipitate was filtered off and air dried. Recrystallization of the crude substance twice from absolute ethanol produced pale yellow needles, m.p. 150–151°. Treatment of this substance with acids, bicarbonates or subliming it failed to remove the mercury.

Anal. Calcd.: for $C_7H_8HgCl_2O_2$: C, 21.25; H, 2.03; Cl, 17.91. Found: C, 20.58; H, 1.82; Cl, 18.22.

Since the analytical results do not agree with the calculated values for the above compound, another run was made and the product recrystallized four times from ethanol. The analysis was C, 20.59; H, 1.69; Cl, 18.15. Obviously, the material was a pure compound with such constancy of composition and no change of melting point, but not of postulated structure.

Peroxide of 2,6-Dimethyl-4-pyrone. To a mixture of 40 ml. of 50% hydrogen peroxide and 30 ml. of water containing ten drops of concentrated sulfuric acid was added 18.6 grams of 2,6-dimethyl-4-pyrone.

The mixture was allowed to stand at room temperature until all the pyrone had dissolved and then gently warmed to 30–40° for 0.5 hr. Storage of the sample in the refrigerator for 24 hr. produced 16.7 g. of white prisms. Five g. of the above sample was heated under reflux with benzene in an all-glass assembly fitted with a Dean-Stark water separator for 90 min. Upon cooling of the benzene solution about 3 g. of heavy spars of the pyrone-peroxide crystallized out, m.p. 95–96.5°, very slow heating.

The peroxide exhibits a peculiar color reaction with dilute solutions of ferric chloride in that a purple color develops after about 10 min., persists for nearly 2 hr. and then gradually fades. Solutions of potassium iodide were slightly discolored by the compound only upon long standing.

Anal. Calcd. for $C_7H_8O_4$: C, 53.84; H, 5.16. Found: C, 54.06; H, 5.45.

(1) F. Feist, *Ann.*, **257**, 253 (1890).
(2) T. Tickle, *J. Chem. Soc.*, **81**, 1004 (1902).
(3) All analyses were performed by Dr. Carl Tiedcke, Teaneck, N. J. All melting points were determined on a Fisher-Johns melting point assembly.

The compound was not acidic. It reacted with benzoyl chloride in benzene after a reflux period of 2 hr. The product, upon analysis, did not have the proper composition for the mono- or dibenzoic ester of any hydroxy compound, alcoholic or phenolic. This test indicated the absence of hydroxyl radicals in the peroxide.

2,6-Dimethyl-3-acetyl-4-pyrone (I). Twelve and four-tenths g. of finely powdered 2,6-dimethyl-4-pyrone, 50 g. of powdered anhydrous aluminum chloride, and 100 ml. of carbon disulfide were quickly and thoroughly shaken in a 500 ml. flask to which was attached a reflux condenser fitted with a gas trap. To the above mixture 15 ml. of acetic anhydride was slowly dropped in. After all the anhydride had been added and the reaction had subsided somewhat the flask was shaken and gently heated for 30 min. The heat was then discontinued and the reaction was allowed to complete itself by standing overnight at room temperature. The carbon disulfide was then decanted from the greyish semisolid and discarded. The residue in the flask was treated with 100 g. of shaved ice followed by 20 ml. of concentrated hydrochloric acid.

The acetylated pyrone was obtained by extracting the resulting solution with benzene and evaporating the solvent. The yield was 3.4 g. The tan solid was recrystallized from boiling heptane and then sublimed to give a pale yellow powder, I, m.p. 125.5–127°.

A mixed melting point of I with an authentic sample of 2,6-dimethyl-4-pyrone was 50–55°.

Anal. Calcd. for $C_9H_{10}O_3$: C, 65.04; H, 6.06. Found: C, 65.34; H, 6.34.

2,4-Dinitrophenylhydrazone of I. One g. each of I and 2,4-dinitrophenylhydrazine were refluxed together in 100 ml. of ethanol for 5 min., filtered into 100 ml. of water containing 20 drops of concentrated hydrochloric acid, and chilled overnight in the refrigerator. The precipitate was recrystallized from absolute ethanol giving 0.8 g. maroon-purple aggregates which sublimed above 180°, softened above 185°, and melted at 189–191°.

Anal. Calcd. for $C_{15}H_{14}N_4O_6$: N, 16.17. Found: N, 16.30.

2,6-Dimethyl-3-acetyl-4-lutidone (II). One g. of I and 20 ml. of ammonium hydroxide were heated in a pressure bottle at 75° for 1 hr. The solution was filtered, evaporated to dryness on a steam bath to a purple solid, and then sublimed to a pale yellow powder which melted at 226–228.5°, rapid heating.

Anal. Calcd. for $C_9H_{11}NO_2$: C, 65.43; H, 6.71; N, 8.47. Found: C, 65.18; H, 7.04; N, 8.24 (Dumas).

2,4-Dinitrophenylhydrazone of II. The 2,4-dinitrophenylhydrazone was prepared by refluxing 1 g. each of II and 2,4-dinitrophenylhydrazine in 50 ml. of absolute ethanol for 5 min. The hydrazone was purified by recrystallizing it twice from absolute ethanol to give 0.3 g., m.p. 203°.

Anal. Calcd. for $C_{15}H_{15}N_5O_5$: N, 20.28. Found: N, 20.44.

2,6-Dimethyl-3-(3,5-dinitrobenzoyl)-4-pyrone [III]. A mixture of 12.4 g. of 2,6-dimethyl-4-pyrone, 21.2 g. of 3,5-dinitrobenzoic acid, 30 g. of fused zinc chloride, and 100 ml. of dry xylene was heated under gentle reflux for 48 hr. The mixture was cooled to −5°C., the xylene decanted, and the black residue vigorously shaken with 100 ml. of boiling water. Extraction with benzene of the residue and evaporation left solid black aggregates which weighed 29 g. The analytical sample, light tan needles, was obtained by recrystallization of 1.5 g. of the compound from 100 ml. of heptane. It melted at 113–114°.

Anal. Calcd. for $C_{14}H_{10}N_2O_7$: C, 52.83; H, 3.16; N, 8.80. Found: C, 52.49; H, 3.40; N, 8.54.

The infrared spectrum[4] of the compound, in chloroform solution, gave an absorption band at 1545 cm.$^{-1}$ for the benzenoid nitro groups. The pyrone structure[5,6] was indicated by a band at 1660 cm.$^{-1}$ An absorption peak at 1715 cm.$^{-1}$ indicated the nonpyrone carbonyl.

2,4-Dinitrophenylhydrazone of the lutidone from III. Two g. of III was dissolved in a small amount of ethanol and then an equal volume of concentrated ammonium hydroxide was added. The solution was allowed to stand overnight in a stoppered flask, following which the mixture was evaporated to dryness on a steam bath. One gram of the grey solid was placed in 100 ml. absolute ethanol along with 1 g. of 2,4-dinitrophenylhydrazine. The mixture was refluxed for 5 min., filtered, and then diluted with an equal volume of water. The orange solid was recrystallized from absolute ethanol, m.p. 199–200.5°.

Anal. Calcd. for $C_{20}H_{16}N_7O_9$: N, 19.71. Found: N, 19.50.

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TEXAS SOUTHERN UNIVERSITY
HOUSTON 4, TEX.

(4) Infrared spectra were determined on a Perkin-Elmer Model 21 Infrared Spectrophotometer.

(5) L. L. Woods, *J. Am. Chem. Soc.*, **75**, 3608 (1953).

(6) L. L. Woods, *J. Am. Chem. Soc.*, **77**, 3161 (1955).

Reactions Between Chloro-*p*-benzoquinones and β-Naphthol

ABDEL-MEGUID OSMAN

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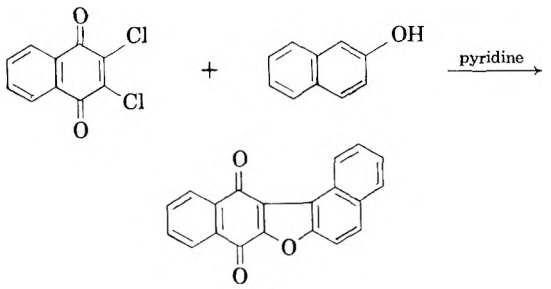
2,3-Dichloro-1,4-naphthoquinone condenses with β-naphthol in the presence of pyridine to give dinaphthylfuranoquinone (I).[1,2]



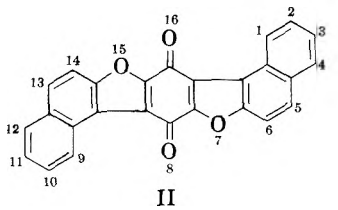
I

The condensation of chloro substituted *p*-benzoquinones with β-naphthol now has been investigated. Thus, when chloranil was allowed to react with β-naphthol in the presence of pyridine, two molecules of the naphthol condensed with one molecule of the quinone to yield a red crystalline substance believed, by analogy to be naphtho-[*1',2'-4,5*]furo[*2,3-h*]benz[*c*]dibenzofuran 8,16-quinone (II). This compound was stable toward heat and oxygen and developed a blue color with concentrated sulfuric acid, a color which is characteristic of brazan- and furanquinones.[1,2] Zinc-dust and glacial acetic acid effected its reduction to the corresponding hydroquinone, the isolation of which

(1) B. Eistert, *Ber.*, **80**, 52 (1927).

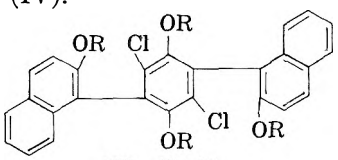
(2) Ng. Ph. Buu Hoï, *J. Chem. Soc.*, 489, 4699 (1952).

has not been attained due to its ready oxidation to the quinone (II) by the action of atmospheric oxygen. Reductive acetylation of II by the action of zinc-dust, acetic acid, and acetic anhydride, yielded the corresponding diacetate. Trials to effect the conversion of II to IV by distillation with zinc-dust or with a zinc-zinc chloride melt[3] were unsuccessful.[4]

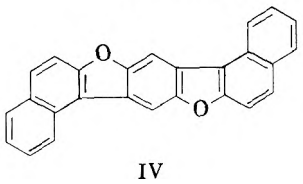


II

Whereas the condensation of chloranil with β-naphthol gave a red crystalline substance, the condensation of 2,5-dichlorobenzoquinone with β-naphthol led to the formation of a colorless substance, believed to have a structure like IIIa. The constitution of IIIa was inferred from the fact that it gave the correct analytical values and the correct molecular weight for the corresponding tetra-acetate (IIIb) obtained by the action of acetic anhydride and fused sodium acetate on IIIa. The ready cyclization of IIIa to the quinone II by boiling in pyridine for a short time involves the elimination of two molecules of hydrogen chloride, followed by oxidation. IIIa, on distillation with zinc-dust in a vacuum, gave a pale yellow substance which analyzed for naphtho[*1',2'-4,5*]furo[*2,3-h*]benz[c]dibenzofuran (IV).



IIIa, R=H
b, R=$COCH_3$



IV

Similarly the condensation of 2-chlorobenzoquinone with β-naphthol in the presence of pyridine yielded a colorless substance; its colorless alcoholic solution turned to deep red by the action of atmospheric oxygen. The condensation product gave a triacetate derivative, showing the presence of three hydroxyl groups. Fractional crystallization of the crude reaction product failed to reveal the presence of any other isomer. The structure of the condensation product is under further investigation.

(3) E. Clar, *Ber.*, **72**, 1645 (1939).

(4) N. Campell and R. S. Gow, *J. Chem. Soc.*, 1555 (1949).

Though the above mentioned reactions of 2,5-dichloro- and of 2-chlorobenzoquinone with β-naphthol are base catalyzed, yet they can be brought about by the action of dilute sulfuric acid.[5,6]

EXPERIMENTAL

Naphtho(1',2'-4,5)furo(2,3-h)benz(c)dibenzofuran 8,16-quinone (II). An intimate mixture of chloranil (0.5 g.) and β-naphthol (0.8 g.) was covered with anhydrous pyridine (about 5 ml.) and the hot reaction mixture was refluxed for a few minutes to complete the reaction. The solution was cooled and the dark red needles were collected, washed thoroughly with alcohol, and then recrystallized from pyridine giving shining deep red needles (0.6 g.), m.p. over 350°. The furan-quinone sublimed unchanged at 320°/5 mm. and gave a blue color with concentrated sulfuric acid.

Anal. Calcd. for $C_{26}H_{12}O_4$: C, 80.41; H, 3.092. Found: C, 80.68; H, 3.24.

Reductive acetylation of the quinone (II). The quinone (0.2 g.) was heated with a mixture of zinc-dust (1 g.), anhydrous sodium acetate (0.5 g.) and acetic anhydride (30 ml.) for 20 min. Excess glacial acetic acid (about 60 ml.) was added and boiling was continued for a further half hour. The clear filtrate was diluted with water and the precipitated colorless crystals were collected and recrystallized from acetic acid giving slender needles, m.p. 310–12°. Yield, theoretical.

Anal. Calcd. for $C_{30}H_{18}O_6$: C, 75.94; H, 3.82. Found: C, 76.09; H, 4.03.

Zinc-dust distillation of the quinone (II). An intimate mixture of one part of the quinone with ten parts of dry zinc-dust was heated *in vacuo*, and the distillate was collected and purified from pyridine forming red needles which gave a blue color with sulfuric acid identical to that given by the quinone III.

The same experiment was repeated with Clar's zinc-zinc chloride melt[3] and the quinone was recovered unchanged.

Reaction between 2,5-dichloro-p-benzoquinone and β-naphthol. (a) *Pyridine as catalyst.* An intimate mixture of 2,5-dichloro-*p*-benzoquinone (0.5 g.) and β-naphthol (1.0 g.) was treated with few drops of anhydrous pyridine and the hot reaction mixture was cooled and stirred till the dark violet color first formed changed to a dirty white (about 20 min). The resulting sticky product was triturated with a few drops of methanol, filtered quickly and washed several times with benzene. Repeated crystallization from a methanol-benzene mixture furnished colorless short rods or rectangular plates of the hydroquinone (Va) (0.5 g.), m.p. 327° (dec.). A solution of the material in organic solvents changed to deep red when left in the air for a short time.

Anal. Calcd. for $C_{26}H_{16}O_4Cl_2$: C, 67.38; H, 3.45; Cl, 15.33. Found: C, 67.63; H, 3.70; Cl, 15.11.

(b) *Dilute sulfuric acid as catalyst.* A suspension of the dichloroquinone (0.2 g.) and β-naphthol (0.4 g.) in 5% acetic acid (40 ml.) was treated with few drops of 10% sulfuric acid and boiled for 2 min. The dark violet solution was cooled and the precipitate was collected, dried thoroughly, and then crystallized from benzene in colorless rectangular plates (0.3 g.), m.p. and mixed m.p. with the product from (a) 326° (dec.).

Tetraacetate IIIb. Acetylation of (IIIa) by the usual methods furnished a colorless tetraacetate which separated from benzene in colorless prisms, m.p. 285°.

Anal. Calcd. for $C_{34}H_{24}O_8Cl_2$: C, 64.65; H, 3.79; Cl, 11.23; Mol. wt. 631. Found: C, 64.22; H, 4.18; Cl, 11.1; Mol. wt. (Rast), 668.

(5) R. Pummerer, *Ber.*, **60**, 1442–51 (1927).

(6) F. M. Dean, A. M. Osman, and A. Robertson, *J. Chem. Soc.*, 11 (1955).

Transformation of IIIa to the quinone (II). A pure sample of the product (IIIa) (0.2 g.) was refluxed in pyridine (7 ml.) for 0.5 hr. The dark red reaction mixture was cooled and the deposited red crystals were collected (0.1 g.) and recrystallized from pyridine into deep red needles, m.p. over 350°. With concentrated sulfuric acid, the mixture gave the blue color characteristic of the quinone (II). The diacetate was prepared by reductive acetylation and proved to be identical with an authentic specimen, m.p. and mixed m.p. 310–312°.

Naphtho(1',2'-4,5)furo(2,3-h)benz(c)-dibenzofuran (IV). An intimate mixture of the hydroquinone (IIIa) and excess zinc was heated *in vacuo*, and the yellow distillate was further purified by sublimation at 300–320°/2 mm. The product was obtained as pale yellow needles, m.p. 300–302° (dec.), giving an intense blue-violet fluorescence in concentrated sulfuric acid or in the organic solvents.

Anal. Calcd. for $C_{26}H_{14}O_2$: C, 87.15; H, 3.91. Found: C, 86.68; H, 3.87.

Reaction between 2-chloro-p-benzoquinone and β-naphthol. A powdered mixture of the chloroquinone (0.5 g.) and β-naphthol (0.7 g.) was moistened with anhydrous pyridine with stirring and cooling. After a few minutes, the reddish paste was triturated with methanol, filtered, washed several times with light petroleum, and crystallized from benzene in colorless needles (0.3 g.), m.p. 260° (dec.), which acquired a reddish tint when exposed to the air.

Anal. Calcd. for $C_{16}H_{11}O_3Cl$: C, 67.01; H, 3.83; Cl, 12.39. Found: C, 67.31; H, 3.93; Cl, 12.67.

The experiment was repeated using dilute sulfuric acid as a catalyst and the same compound was obtained as shown by m.p. and mixed m.p. determinations.

The reaction product was acetylated in the usual manner and the resulting triacetate was recrystallized from benzene into colorless needles, m.p. 262°.

Anal. Calcd. for $C_{22}H_{17}O_6Cl$: C, 64.0; H, 4.12; Cl, 8.60. Found: C, 63.71; H, 4.18; Cl, 9.10.

CHEMISTRY DEPARTMENT
FACULTY OF SCIENCE
A'IN-SHAMS UNIVERSITY
ABBASSIA, CAIRO, EGYPT

Synthesis of 1-Phenyl-5-aminotetrazole from Benzaldehyde and Hydrazoic Acid

WM. H. HOUFF

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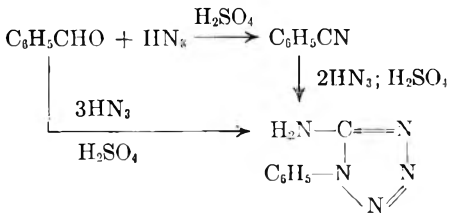
The formation of 1,5-disubstituted tetrazoles by the Schmidt reaction employing excess hydrazoic acid on ketones is well established.[1] Acetone and hydrazoic acid, for example, yield 1,5-dimethyltetrazole[2] although not in the excellent yields originally reported.[3] The action of excess hydrazoic acid on aldehydes has been only slightly studied.[4,5] Benzaldehyde is reported to yield 1-phenyltetrazole[4] while 2-thiophenaldehyde apparently yields 1-(2-thienyl)tetrazole.[5] Since the identification of the products was incomplete in both cases the present investigation was undertaken.

In the presence of concentrated sulfuric acid, equimolar quantities of aldehydes and hydrazoic acid produce nitriles.[1] Under similar conditions 1-substituted-5-aminotetrazoles result from the interaction of nitriles with hydrazoic acid.[6,7] The combination of the two reactions into a single step employing excess hydrazoic acid might be expected to yield 1-substituted-5-aminotetrazoles.

Under similar conditions the reactions of benzaldehyde with one- and three-mole quantities of hydrazoic acid and of benzonitrile with two moles of hydrazoic acid in the presence of concentrated sulfuric acid were studied. From equimolar amounts of benzaldehyde and hydrazoic acid the expected product, benzonitrile, was isolated. Benzonitrile, in turn, reacts with two moles of hydrazoic acid yielding 1-phenyl-5-aminotetrazole. The interaction of benzaldehyde with excess hydrazoic acid also gave 1-phenyl-5-aminotetrazole.



Other aldehydes, including cinnamaldehyde, 1-naphthaldehyde, and *n*-butyraldehyde were examined. However, in no case could an identifiable product be isolated after interaction with excess hydrazoic acid. Intractable tars were the invariable result.

EXPERIMENTAL

Benzonitrile from benzaldehyde. Sulfuric acid (40 g.) was added slowly to a stirred solution of 10.6 g (0.1 mole) of benzaldehyde contained in 110 ml. of 1.0*N* hydrazoic acid in benzene. During the addition the temperature of the mixture was controlled at 35–40°. Evolution of nitrogen ceased in about 30 min. The solution was allowed to stand an additional 30 min. and 200 ml. of ice water was added. After extraction with 2% sodium hydroxide solution the benzene layer was dried over anhydrous sodium sulfate. The benzene was removed by evaporation and the resulting oil was distilled to yield 7.9 g. (77%) of benzonitrile, b.p. 190.5–191°; n_D^{25} 1.5286.

1-Phenyl-5-aminotetrazole from benzonitrile. In a procedure similar to one previously described[7] 40 g. of concentrated

(1) H. Wolff, "The Schmidt Reaction," Chapter 8 in R. Adams, "Organic Reactions," John Wiley & Sons, New York, 1946, Vol. III, p. 308.

(2) Schmidt, U. S. Patent 1,599,493 [*Chem. Abstr.*, 20, 3460 (1926)].

(3) Harvill, Herbst, Schreiner, and Roberts, *J. Org. Chem.*, 15, 662 (1950).

(4) Schmidt and Zutavern, Ger. Patent 455,585 [*Chem. Abstr.*, 21, 3057 (1927)].

(5) Houff, Ph.D. Thesis, Michigan State University, E. Lansing, Mich. (1955).

(6) V. Braun and Keller, *Ber.*, 65, 1677 (1932).

(7) Herbst, Roberts, and Harvill, *J. Org. Chem.*, 16, 139 (1951).

sulfuric acid was added dropwise to a stirred solution of 10.3 g. (0.1 mole) of benzonitrile dissolved in 250 ml. of 1.0*N* hydrazoic acid in benzene. After an elapsed time of 3 hr. the reaction mixture was poured over 100 g. of crushed ice. The aqueous layer was neutralized with 40% sodium hydroxide solution causing the separation of a crude crystalline solid. A single recrystallization from ethanol gave 5.9 g. (37%) of 1-phenyl-5-aminotetrazole; m.p. 160.5–161.5° (reported[7] 159.5–160°).

Anal. Calcd. for $C_7H_7N_5$: N, 43.5. Found: 43.7.

1-Phenyl-5-aminotetrazole from benzaldehyde. Under reaction conditions similar to those described above, 10.6 g. (0.1 mole) of benzaldehyde dissolved in 330 ml. of 1.0 *N* hydrazoic acid in benzene solution was treated dropwise with 40 g. of concentrated sulfuric acid. The temperature of the reaction mixture was maintained at 35–40° for 5 hr. during which gas evolution ceased. The greenish colored reaction mixture was poured over ice and the product was isolated as described in the preceding procedure. After a single recrystallization from ethanol there was received 4.7 g. (30%) of 1-phenyl-5-aminotetrazole; m.p. 159.5–160.5°.

Anal. Calcd. for $C_7H_7N_5$: N, 43.5. Found: 43.4.

Mixtures of 1-phenyl-5-aminotetrazole prepared from benzonitrile and benzaldehyde had m.p. 160°–160.5°.

F. C. Huyck & Sons Research Laboratories
Kenwood Mills
Rensselaer, N. Y.

Reaction of Silver 4-Hydroxyvalerate with Bromine

Jean B. Umland[1] and Sonia A. Witkowski

Received August 31, 1956

In the course of other work in this laboratory the conversion of *cis*-2-hydroxycyclopentaneacetic acid to *cis*-2-methylcyclopentanol by way of the Hunsdiecker silver salt–bromine degradation was attempted. No carbon dioxide was evolved. Although Oldham and Ubbelohde[2] have suggested that hydroxylic compounds other than water might prevent the decarboxylation reaction from taking place, no investigation appears to have been made of the claim of Hunsdiecker, Hunsdiecker, and Vogt[3] that the reaction proceeds normally with hydroxy acids in which the hydroxyl group is not in the α- position to form hydroxyalkylhalides poorer by one C-atom.

When the reaction of methyl silver adipate with bromine,[4] which in this laboratory gave a 63% yield of methyl 5-bromovalerate, was carried out in the presence, of an equimolar quantity of cyclopentanol, little, if any, carbon dioxide was evolved and none of the desired product was obtained. The cyclopentanol contained 0.088% water; addition of three times this amount of water did not prevent decarboxylation although the yield of methyl 5-bromovalerate was only 43%. Therefore an alcoholic hydroxyl group does indeed prevent decarboxylation.

To determine what products are formed by the reaction of the silver salt of a hydroxy acid in which the hydroxyl group is not in the α- position with bromine, the reaction of silver 4-hydroxyvalerate, prepared from commercially available γ-valerolactone, was investigated. By the salt-to-bromine addition method at 0° a 36% yield of levulinic acid and a 23% yield of γ-valerolactone were obtained along with a small amount of a volatile organic acid which was not identified. No carbon dioxide was formed. By the bromine-to-salt addition method in refluxing carbon tetrachloride the yield of levulinic acid was 18% and of γ-valerolactone 46%. In addition to the small amount of volatile acid, a small quantity of a neutral material, which decomposed on distillation, was formed and a maximum of 2.5% of carbon dioxide was evolved. In both cases the remainder of the product was nonvolatile and acidic and may well have consisted largely of levulinic acid.

EXPERIMENTAL[5]

Reaction of silver 4-hydroxyvalerate with bromine. A solution of 19.8 g. (0.30 mole) of potassium hydroxide in 90 ml. of water was refluxed for one hour with 28 ml. (0.30 mole) of γ-valerolactone. The solution was then cooled and neutralized to *p*H 8 with a few drops of 6*N* nitric acid and a solution of 51.0 g. (0.30 mole) of silver nitrate in 60 ml. of water was added rapidly with stirring and cooling. After about 10 min. the silver 4-hydroxyvalerate was collected on a Büchner funnel and sucked as dry as possible. It was then washed thoroughly by trituration first with methyl alcohol and then with ether, removing the solvents by suction filtration, and dried 24 hr. at room temperature[6] in a vacuum desiccator over Drierite at <1 mm. in the dark. A 90% yield was obtained.

The silver salt (0.27 mole) was finely powdered, placed in the flask from which it was to be added, and dried another 24 hr. over phosphorus pentoxide instead of Drierite. It was then added in small portions to a stirred solution of *ca.* 16 ml. (0.31 mole) of dry[7] bromine in 150 ml. of dry[8] carbon tetrachloride cooling in an ice bath during a period of 70 min. After addition of the silver salt was complete, the reaction mixture was allowed to warm to room temperature. No carbon dioxide was detected when the flask was swept out with dry, carbon dioxide-free nitrogen, which was then passed through a weighed Ascarite tube. The silver bromide was isolated by filtration, washed thoroughly first with hot carbon tetrachloride and then with water, and air-dried; the yield was 94%.

The excess bromine was destroyed with sodium bisulfite and the carbon tetrachloride solutions were washed with an

(1) Inquiries should be addressed to this author at 211 Scherrer St., Cranford, N. J.

(2) J. W. H. Oldham and A. R. Ubbelohde, *J. Chem. Soc.*, 368 (1941).

(3) H. Hunsdiecker, C. Hunsdiecker, and E. Vogt, U. S. Patent 2,176,181 (1939).

(4) C. F. H. Allen and C. V. Wilson, *Org. Syntheses*, **Coll. Vol. 3,** 578 (1955).

(5) Melting points were determined in open borosilicate glass capillaries using a Hershberg apparatus and are corrected unless otherwise noted.

(6) Silver 4-hydroxyvalerate darkens rapidly when heated.

(7) Bromine was dried by shaking with concentrated sulfuric acid followed by distillation from phosphorus pentoxide.

(8) Carbon tetrachloride was dried by distillation and stored over phosphorus pentoxide.

excess of cold 20% potassium carbonate. The aqueous solutions, which were kept cold, were saturated with potassium carbonate and extracted with carbon tetrachloride. The carbon tetrachloride solutions were combined, dried for 1 hr. over potassium carbonate, and fractionated with a Holzman column at atmospheric pressure. After removal of the carbon tetrachloride, 0.6 g. of material boiling between 77.0° and 200° was obtained. The residue was distilled from a Claisen flask at reduced pressure. A 23% yield of γ-valerolactone was obtained, b.p. *ca.* 92.5–94° (19 mm.); n_D^{25} 1.4326.

Anal. Calcd. for $C_5H_8O_2$: Sapon. equiv., 100. Found: Sapon. equiv., 98.

The phenylhydrazide, prepared according to the procedure given by Huntress and Mulliken,[9] melted at 76.0–77.0°. The phenylhydrazide of an authentic sample of γ-valerolactone, b.p. *ca.* 96° (21 mm.), n_D^{25} 1.4319, was obtained in the same yield and melted at 76.8–77.0°. The melting point of a mixture of the two derivatives was not depressed.

Only 0.6 g. of material remained in the flask at the end of the distillation.

The water layers were strongly acidified with phosphoric acid and steam distilled. The first two liters of steam distillate contained sulfur dioxide, but gave negative tests[10] for halide, phosphate, and a sulfate and the sodium salt gave negative tests for carbonate and nitrate and burned on ignition. The sulfur dioxide was determined as described by Treadwell and Hall[11] and the acidity due to it was subtracted from the total acidity to obtain the amount of organic acid. The first liter of steam distillate contained 17.2 meq. of organic acid, the second 1.7, the third 1.3, and the fourth 1.1 making a total of 21.3 meq. or an 8% yield of volatile acid. Since this acid was undoubtedly contaminated with levulinic acid, which is slightly volatile with steam, and the amount formed was small, it was not identified and steam distillation was stopped. Water was removed at water pump pressure and the residue was extracted with boiling benzene. Distillation of the benzene extract gave 8.1 g. (26%) of levulinic acid, b.p. *ca.* 150–152.5° (20 mm.).

Anal. Calcd. for $C_5H_8O_3$: Neut. equiv., 116. Found: Neut. equiv., 118.

The 2,4-dinitrophenylhydrazone, which was prepared according to the procedure of Cowley and Schuette,[12] melted at 206.6° (uncorr.). The 2,4-dinitrophenylhydrazone of an authentic sample of levulinic acid, b.p. *ca.* 150–151° (20 mm.), melted at 206.6° (uncorr.). The melting point of a mixture of the two derivatives showed no depression.

Only 0.7 g. of material remained in the pot at the end of the distillation.

An additional 10% of levulinic acid was obtained from the residue by extraction with alcohol.

When the reaction was carried out by adding bromine to a stirred suspension of 0.27 mole of silver salt in 150 ml. of carbon tetrachloride without cooling, a mildly exothermic reaction occurred. About 8 ml. (0.16 mole) of bromine was required to give a permanent yellow color; it was added over a period of 42 min. The reaction mixture was then refluxed for 30 min. Three tenths of a gram of material was absorbed on the Ascarite which corresponds to a 2.5% yield of carbon dioxide. However, some of this material was probably bromine as a little bromine vapor was swept through the absorption tube. (Some carbon dioxide was formed as in a similar experiment where the vapors were passed through lime water, the lime water turned milky.) The reaction mixture was worked up as described above; a 94% yield of silver bromide was obtained. The following fractions were obtained from the carbon tetrachloride solutions: 0.9 g. b.p. 80–90°; 1.8 g., b.p. 90–110° (decomp.); 0.4 g., b.p. 110–193°. Distillation of the residue gave a 46% yield of γ-valerolactone, b.p. *ca.* 95–105° (20 mm.). A 7% yield of volatile acid was obtained. Distillation of the benzene extract gave 5.7 g. (18%) of impure levulinic acid, b.p. *ca.* 148–158° (20 mm.); 2.0 g. of material remained in the pot. An attempt to isolate more levulinic acid from the residue by extraction with alcohol was unsuccessful.

CARR LABORATORY
MOUNT HOLYOKE COLLEGE
SOUTH HADLEY, MASS.

(9) E. H. Huntress and S. P. Mulliken, *Identification of Pure Organic Compounds Order I*, John Wiley and Sons, Inc., New York, 1941, p. 353.

(10) C. H. Sorum, *Introduction to Semimicro Qualitative Analysis*, Prentice-Hall, Inc., New York, 1949, pp. 152–161.

(11) F. P. Treadwell and W. T. Hall, *Analytical Chemistry*, 9th English ed., John Wiley and Sons, Inc., New York, 1942, p. 322.

(12) M. A. Cowley and H. A. Schuette, *J. Am. Chem. Soc.*, **55**, 3463 (1933).

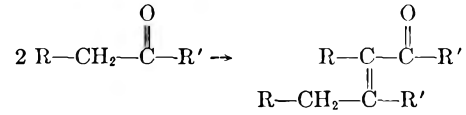
Ketone Condensations Using a Sulfonic Acid Ion Exchange Resin

N. B. LORETTE

Received September 4, 1956

The self-condensation of ketones to α,β-unsaturated ketones has been carried out using numerous catalysts. Wayne and Adkins[1] list (with references) 14 different reagents used to catalyze this type of condensation. The first to use cation exchange resin as a condensation catalyst was Durr.[2] He used Amberlite IR 120 and reported the condensation of cyclohexanone to 2-cyclohexylidenecyclohexanone in 20% yield. Reese[3] showed that the acid catalyzed condensation of cyclohexanone gave 2-(1-cyclohexenyl)cyclohexanone. This was found to be the main product of the Dowex 50 catalyzed condensation of cyclohexanone and was probably what Durr had rather than 2-cyclohexylidenecyclohexanone. Klein and Banchero[4] determined the reaction rate for the condensation of acetone directly to mesityl oxide using a sulfonic acid cation exchange resin (Dowex 50) as the catalyst.

Additional work has been carried out using the above two ketones and three other ketones. With the exception of cyclohexanone, the following general equation illustrates the condensation:



The reaction rates are low and long periods of time are required. However, this is counterbalanced by the simplicity of the technique and by the good yields obtained.

(1) W. Wayne and H. Adkins, *J. Am. Chem. Soc.*, 62, 3401(1940).

(2) G. Durr, *Compt. rend.*, **236**, 1571 (1953).

(3) J. Reese, *Ber.*, **75**, 384 (1942).

(4) F. G. Klein and J. T. Banchero, *Ind. Eng. Chem.*, **48**, 1278 (1956).

EXPERIMENTAL

Acetone. Twelve hundred g. of acetone (commercial grade) was charged in a 2-l. distillation pot which was equipped with a thermowell and an inlet tube. The pot was attached to a 30-in. column. Between the overhead discharge of the column and the pot inlet tube was placed a catalyst bed. This consisted of 500 ml. of acetone-washed Dowex 50 (hydrogen form) in an insulated 45 × 450 mm. borosilicate glass tube. Boiling of the pot material caused the acetone vapors to pass through the column, over the catalyst and back into the distillation pot. The initial rate of acetone passing over the catalyst was 300 ml. per hour. The rate became lower as the acetone concentration diminished. Progress of the reaction was followed by the rise in pot temperature. At the beginning of the run the pot temperature was 57.8°, while at the end of the run (117 hr.) it was 87°. Distillation of the crude products gave 152 g. of acetone, 464 g. of mesityl oxide–water azeotrope, and 399 g. of mesityl oxide. This is an acetone conversion of 87.4% and a yield of mesityl oxide of 79.4% based on converted acetone.

Ethyl methyl ketone. This ketone was condensed using the same procedure and apparatus that was used for acetone. Eleven hundred ninety-six g. of ethyl methyl ketone was used. The hot vapors maintained a resin bed temperature of 70–80°. After 50 hr. the pot temperature had risen only 3.6°. (The water formed during the condensation was being recycled over the resin by means of the ethyl methyl ketone–water azeotrope, thereby inhibiting further condensation.) By distillation, 942 g. of ethyl methyl ketone and 199 g. of C_8 unsaturated ketone boiling from 77 to 83° at 50 mm. was recovered. The C_8 cut, which was a mixture of the two possible isomers, 5-methyl-4-hepten-3-one and 3,4-dimethyl-3-hexen-2-one, was redistilled at atmospheric pressure. It boiled at 155 to 167°. Molecular weight determination (by benzene freezing point depression) of a cut boiling at 158 to 161° was 127, for a cut boiling at 165 to 167° was 130; theoretical is 126. The refractive index ranged from n_D^{23} 1.4405 for the 155° material to n_D^{23} 1.4460 for the 165 to 167° cut. No effort was made to separate the two isomers quantitatively.

3-Pentanone. Twenty g. of Dowex 50 (hydrogen form) and 660 g. of 3-pentanone were placed in a 1-l. flask equipped with a magnetic stirrer and heated by the top half of a Glas-Col hemispherical heating mantle (to prevent bumping). The pot was attached to a 30-in. column. A system pressure of 200 to 300 mm. was maintained so that boiling could occur without the pot temperature reaching a point where the resin would decompose. This pressure effected pot temperatures of 50 to 75°. The system was operated under total reflux most of the time. Periodically 3-pentanone–water azeotrope cuts of 5 to 20 ml. were taken. After 54 hr. the reaction was stopped and the pot material freed of the catalyst by filtration. Distillation of the filtrate yielded 537 g. of 3-pentanone and 56 g. of 5-ethyl-4-methyl-4-hepten-3-one, b.p. 84–86° at 20 mm, d_{24} 0.856; lit.[1] b.p. 101–104° at 44 mm., d_4^{28} 0.8552.

Cyclohexanone. Twenty-one g. of dry Dowex 50 (hydrogen form) and 545 g. of cyclohexanone were charged in a 1-l., 3-necked flask equipped with a thermometer, condenser, outlet tube, and magnetic stirrer. A pot temperature of 70 to 80° was maintained. About 3 times each day for 1-hr. periods dry ($CaCl_2$) air was drawn in through the condenser, above the liquid and out the outlet tube into a dry ice trap. Water and cyclohexanone vapors were condensed forming two layers. The cyclohexanone was separated and returned to the reaction pot. During the 51.5-hr. run, progress of the reaction was followed by the refractive index change. The initial reading was n_D^{25} 1.4472 and the final was n_D^{25} 1.4960. Distillation of the filtered products yielded 142 g. of cyclohexanone and 268 g. of 2-(1-cyclohexenyl)cyclohexanone, b.p. 125° at 7 mm.; n_D^{18} 1.5072, n_D^{60} 1.4912; lit.[4], n_D^{60} 1.4918.

Acetophenone. Twenty-three g. of Dowex 50 (hydrogen form) and 618 g. of acetophenone were charged in a one-liter, 3-necked flask equipped with a magnetic stirrer. The reaction mixture was maintained at 70–75°. Water was removed from the reaction mixture as in the manner described for cyclohexanone. The refractive index of the mixture increased from an initial n_D^{25} 1.5310 to n_D^{25} 1.5670 after 246 hr. The crude products were freed of the resin by filtration and then distilled to yield 361 g. of acetophenone and 140 g. of yellow dypnone, b.p. 136–139° at 1 mm.; lit.[1] b.p. 138–140° at 1 mm. On cooling, 50 g. of 1,3,5-triphenylbenzene (m.p. 169°) precipitated from the distillation residue.

ORGANIC BASIC RESEARCH LABORATORY
THE DOW CHEMICAL COMPANY
FREEPORT, TEX.

Convenient Preparation of α-Deuterated Acids[1]

CHARLES C. PRICE,[2] ERNEST L. ELIEL,[3] AND ROBERT J. CONVERY

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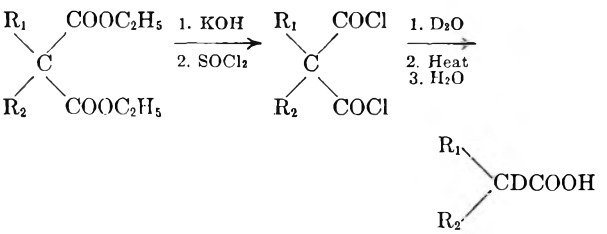
The conversion of malonic acids to the acid chlorides, followed by hydrolysis with heavy water and decarboxylation, affords a convenient procedure for the preparation of α-deuterated aliphatic and alicyclic acids offering advantages over previous procedures.[4]

α-Deutero-isobutyric and -hexahydrobenzoic acid have been prepared by the following sequence of reactions:



The yields and properties of the intermediate compounds and final products are listed in Table I.

The deuterated acids were found to have some marked differences in infrared spectra from the unlabeled analogs. These data will be presented elsewhere.

(1) Abstracted in part from the Master's Dissertation of R. J. Convery, University of Notre Dame, Notre Dame, Ind., supported in part by the Radiation Project, University of Notre Dame, through A.E.C. Contract No. At(11-1)-38.

(2) Present address, University of Pennsylvania, Philadelphia 4, Pa.

(3) Present address, University of Notre Dame, Notre Dame, Ind.

(4) C. C. Price and H. Morita, *J. Am. Chem. Soc.*, **75**, 3686 (1953); D. G. Hill, B. Stewart, S. W. Kantor, W. A. Judge, and C. R. Hauser, *J. Am. Chem. Soc.*, **76**, 5129 (1954).

TABLE I

Substituents	$R_1 = R_2 = CH_3$	$R_1 + R_2 = (CH_2)_5$
Diethyl malonate	84% yield[6] b.p. 83° (18 mm.)–85° (19 mm.) (lit. 196.5°)[5]	50% yield[7] b.p. 74–77° (0.3 mm.) (lit. 105–106° 5 mm.)[7]
Malonic acid	90% yield m.p. 191–192° (dec.) (lit. 193–194°, dec.)[5]	70% yield m.p 170–171° (dec.) (lit. 176°, dec.)[8]
Malonyl chloride	76% yield b.p. 156–159° (lit. 165°)[9]	68% yield b.p. 67–69° (0.7 mm.)
α-Deuterated acid	58% yield (from the malonyl (chloride) b.p. 151.8–152.2° (lit. 153.5–154.4°)[10] 1.07 atoms of deuterium per molecule of acid[12]	53% yield (from the malonyl chloride) b.p. 90.0–90.5° (1 mm.) (lit. 232.5°)[11] 1.05 atoms of deuterium pr molecule of acid[13]

EXPERIMENTAL

Hydrolysis of malonic ester.[5] The malonic ester (1 mole) is refluxed for 20 hr. with a 25% alcoholic potassium hydroxide (4 moles) solution. The reaction mixture is cautiously distilled and 60–75% of the alcohol is collected. Water (a volume equal to one-half of the original volume of alcohol in the reaction mixture) is added to the residue and the distillation is continued until all of the alcohol is removed. The residue is extracted with ether to remove any unreacted ester.

The residue is cooled and cautiously acidified with concentrated hydrochloric acid. The acidified mixture is extracted with ether. The ether is evaporated from the solution and the residue is dried in a vacuum dessicator.

Preparation of malonyl chloride. A mixture of the malonic acid 1 mole) and thionyl chloride (5 moles) is refluxed for 20 hr The excess thionyl chloride is distilled from the reaction m ixture and the crude acid chloride is distilled.

Hydrolysis of malonyl chloride with heavy water and decarboxylation of the deuterated malonic acid. A mixture of the malonyl chloride and 99.5% deuterium oxide (15% excess) is cautiously refluxed for 2 hr. The mixture is heated to 30° below the melting point of the malonic acid to remove the excess water. The residue is cautiously heated to 15–20° degrees above the melting point of the malonic acid until no more gas is evolved.

The crude α-deuterated acid is dissolved in hot water and the solution is refluxed to exchange the deuterium of the carboxylic acid group. The α-deuterated acid is separated from the water and distilled.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF NOTRE DAME
NOTRE DAME, IND.

(5) J. F. Norris and H. F. Tucker, *J. Am. Chem. Soc.*, **55**, 4700 (1933).

(6) L. T. Thorne, *J. Chem. Soc.*, **39**, 543 (1881).

(7) A. W. Dox and L. Yoder, *J. Am. Chem. Soc.*, **43**, 1366 (1921).

(8) W. A. Wightaman, *J. Chem. Soc.*, 2541 (1926).

(9) H. Staudinger and St. Bereza, *Ber.*, **41**, 4463 (1908).

(10) W. Markownikow, *Ann.*, **138**, 368 (1866).

(11) J. S. Lumsden, *J. Chem. Soc.*, **87**, 90 (1905).

(12) Calculated from the densities of the deuterated (d^{25}_4 0.9594) and undeuterated (d^{25}_4 0.9478) acids according to the formula of McLean and Adams, *J. Am. Chem. Soc.*, **58**, 864 (1936).

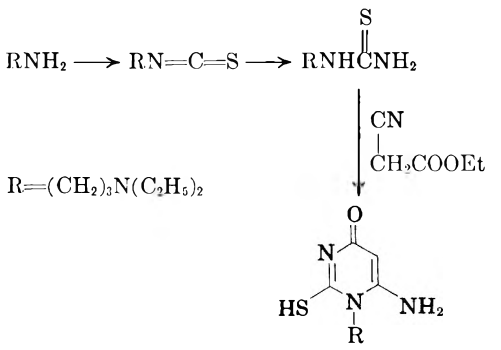
(13) The acid was converted to the methyl ester which was analyzed for deuterium by densities. A mixture (d^{25}_4 0.9753) was prepared from 2.20 g. of the deuterated ester and 7.79 g. of the undeuterated ester (d^{25}_4 0.9736).

An N-Dialkylaminoalkylpyrimidine[1]

ACHINTYA K. SEN AND CHARLES C. PRICE

Received September 10, 1956

A sample of 6-amino-1-(3-diethylaminopropyl)-2-mercapto-4-(1H)pyrimidone has been prepared by the following sequence.



EXPERIMENTAL

3-Diethylaminopropyl isothiocyanate. To a stirred mixture of 20 ml. of water and 7.6 g. (0.1 mole) of carbon disulfide in an ice bath, 13.0 g. (0.1 mole) of 3-diethylaminopropylamine was added during 45 min. After the addition the mixture was stirred at that temperature for 0.5 hr. The ice bath was removed and 10.9 g. (0.1 mole) of ethyl chlorocarbonate was added to the mixture over a period of 1 hr. The solid dithiocarbamate derivative which had earlier separated gradually went into solution at this stage. After stirring for 30 min. more the solution was transferred to a separatory funnel and basified with a slight excess of concentrated aqueous caustic soda solution. The upper oily layer was separated and the aqueous portion was extracted once with ether. The combined organic layers were dried with magnesium sulfate and ether was removed at atmospheric pressure. The residue was fractionally distilled *in vacuo*, yielding 10 g. (58%) of colorless liquid boiling at 95° (3.5 mm.), (n^{25}_D 1.4968).

Anal. Calcd. for $C_8H_{16}N_2S$: C, 55.81; H, 9.30; N, 16.28; S, 18.60. Found: C, 55.51; H, 9.46; N, 16.30; S, 18.40.

3-Diethylaminopropylthiourea. A mixture of 10 ml. of concentrated ammonium hydroxide solution and 10 g. (0.058 mole) of 3-diethylaminopropylisothiocyanate was heated on a steam bath for 30 min., cooled, and treated with 10 ml. of acetone. On scratching, the thiourea was obtained as a white crystalline solid (10 g., 91%) melting at 97°. After recrystallization from acetone, the thiourea melted at 98°.

Anal. Calcd. for $C_8H_{19}N_3S$: C, 50.79; H, 10.06; N, 22.22; S, 16.92. Found: C, 50.87; H, 9.93; N, 22.20; S, 17.00.

6-Amino-1-(3-diethylaminopropyl)-2-mercapto-4-(1H)-pyrimidone. 3-Diethylaminopropylthiourea (9.5 g., 0.05 mole) was dissolved in a solution of sodium ethoxide in ethanol pre-

(1) This work was supported by Public Health Service Grant C-2189, to the University of Pennsylvania.

pared from 1.85 g. (0.08 mole) of sodium in 25 ml. of absolute ethanol. To the cooled solution, 6 g. (0.053 mole) of ethyl cyanoacetate was added and the mixture was refluxed for 2 hr. After the period was over the mixture was cooled, 30 ml. of water was added and the resulting solution was neutralized with an equivalent quantity of acetic acid. The pyrimidine derivative (9.5 g., 74% yield) was collected and washed with water. Recrystallization from ethyl alcohol yielded white shining crystals melting at 215–216°.

Anal. Calcd. for $C_{11}H_{20}ON_4S$: C, 51.56; H, 7.81; N, 21.88; S, 12.50. Found: C, 51.66; H, 7.69; N, 21.90; S, 12.05.

JOHN HARRISON LABORATORY OF CHEMISTRY
UNIVERSITY OF PENNSYLVANIA
PHILADELPHIA, PA.

Isotopically Labeled β-Aminopropionitrile[1]

E. D. SCHILLING[2] AND F. M. STRONG

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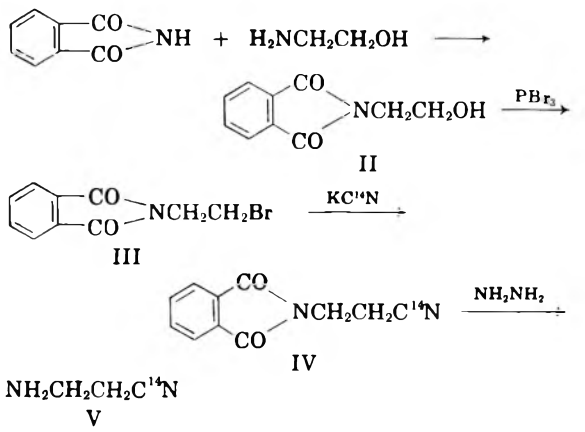
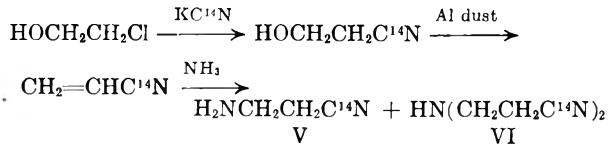
Following the demonstration that β-(N-γ-L-glutamyl)aminopropionitrile (I) is the natural causative agent of the skeletal deformities produced in rats by *Lathyrus odoratus* seeds,[3] it was readily established that the toxicity was due to the β-aminopropionitrile (BAPN) portion of the molecule.[4–6] As a possible aid in studying the mechanism by which BAPN causes the breakdown of mesenchymal tissues, isotopically labeled material was needed.

BAPN containing N^{15} in the amino group was obtained by reacting N^{15} phthalimide with acrylonitrile to produce β-phthalimidopropionitrile, which was then cleaved with hydrazine.[7] The preparation of BAPN containing C^{14} in the nitrile group (V) was first attempted *via* the following route:



Unexpected difficulty was encountered in the replacement of the bromine atom of III with cyanide. Only traces of the desired product, IV, could be isolated from the reaction mixture. Variations in the reaction conditions were studied, and the chloro and iodo analogs of III were prepared and tried, but the only product obtained was the hydroxy compound II. Since hydrolysis of the halogen appeared to be the main reaction, a nonaqueous solvent, N,N-dimethylformamide, was tried and did give a small amount of IV. However, the yield was too low to be desirable for use with C^{14} materials.

Two other possible routes to V were rather cursorily attempted without success. Bubbling gaseous hydrogen cyanide slowly through ethylene imine, evaporating the excess reagents, and adding ethanolic hydrochloric acid gave only an uncrystallizable gum. No catalysts were tried. As far as the authors are aware this direct and obvious approach to BAPN has not been investigated. Reaction of β-chloroethylamine hydrochloride with inorganic cyanide likewise yielded only polymeric material. The desired compound was eventually obtained as follows:



Although the yields were still not high, this method had the advantage of simultaneously producing the labeled bis compound, VI, which was also desired for metabolic studies.

EXPERIMENTAL

β-Aminopropionitrile-amino-N^{15}. Potassium N^{15} phthalimide (Eastman) containing 34% N^{15} was dissolved in water and treated with hydrochloric acid. The free phthalimide was filtered off and thoroughly dried. A mixture of 9.6 g. of this product and 33 ml. of acrylonitrile was refluxed for 10 min. on a steam bath, then 1.0 ml. of a 40% solution of benzyltrimethylammonium hydroxide (Triton B) in methanol was gradually introduced beneath the surface of the refluxing liquid over a period of 15 min. The solution was introduced through a capillary and was forced into the reaction mixture under mild air pressure. Removal of excess acrylonitrile from the resulting clear yellow solution by distillation under reduced pressure left an essentially quantitative yield of β-phthalimidopropionitrile (IV) as a mass of granular yellow crystals. A small portion was decolorized with charcoal in boiling 70% ethanol solution and then crystallized from this solvent to yield colorless crystals, m.p. 151–152°, unchanged after four recrystallizations. Galat[8] reports m.p. 154–155.5°.

To effect hydrazinolysis, 11.7 g. of the crude yellow product, 1.9 g. of anhydrous hydrazine, and 42 ml. of 95% etha-

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(2) Du Pont Predoctoral Fellow, 1955–56.

(3) E. D. Schilling and F. M. Strong, *J. Am. Chem. Soc.*, **77**, 2843 (1955).

(4) T. E. Bachhuber, J. J. Lalich, D. M. Angevine, E. D. Schilling, and F. M. Strong, *Proc. Soc. Exp. Biol. Med.*, **89**, 294 (1955).

(5) W. Dasler, *ibid.*, **88**, 196 (1955).

(6) S. Wawzonek, I. V. Ponseti, R. S. Shepard, and L. G. Wiedenmann, *Science*, **121**, 63 (1955).

(7) A. A. Goldberg and W. Kelly, *J. Chem. Soc.*, 1369 (1947).

(8) A. Galat, *J. Am. Chem. Soc.*, **67**, 1414 (1945).

nol were mixed, warmed to 50° for 10 min., allowed to stand 1 hr. at room temperature, and then reheated to 60°, and concentrated hydrochloric acid was added with stirring until the *p*H dropped to 1. The mixture was stirred and heated at 60° for 2 hr. longer and then cooled in an ice bath. The precipitated phthalhydrazide was filtered off and the filtrate was adjusted to pH 10 with saturated aqueous sodium hydroxide solution. The basic solution was mixed with 2 g. of sodium chloride and extracted with ether for 5 hr. in a continuous extractor, and the extract was dried over anhydrous potassium carbonate. Concentration of the extract to a small volume and addition of 5% ethanolic hydrochloric acid caused the precipitation of 2.54 g. (4[illegible]%) of BAPN hydrochloride, m.p. 165–166°. The m.p. of this salt has been reported to be 164°.[9] Analysis with the mass spectrometer showed 15.4 atom per cent N^{15} excess in this product.[10]

β-Aminopropionitrile-1-C.[14] C^{14} Barium carbonate was converted to C^{14} potassium cyanide by the method of McCarter.[11] Yields varied from 82 to 84%.

A mixture of the radioactive potassium cyanide from 100 mg. of barium carbonate (specific activity 1 mc. per millimole), 14.8 g. of nonradioactive potassium cyanide, and 19.5 g. of ethylene chlorohydrin was stirred continuously at 55° and 6.5 ml. of water was added dropwise during a period of 1.75 hours.[12] Stirring was continued while the mixture was maintained at 55° for 45 min. after addition of the water was complete and then at 60° for 3 hr. longer. The reaction mixture was then extracted five times with 15-ml. portions of acetone, and the extract was fractionally distilled. Ethylene cyanohydrin distilled as a colorless liquid, 7.48 g. (44%), b.p. 223–224°.

The above product and 0.75 g. of aluminum dust were placed in a 50-ml. conical flask fitted with a reflux condenser and with a second condenser arranged for downward distillation.[12] Steam was passed through the reflux condenser and the flask was heated in an oil bath at 180° until distillation ceased (*ca.* 3 hr.). The distillate was collected in a centrifuge tube chilled in dry ice. The oil bath temperature was then raised to 280° and held there until dehydration was complete (total heating time 8 hr.). Decantation of the upper oily layer in the receiver from the lower frozen water layer gave 4.4 g. (79%) of radioactive acrylonitrile.

This material without further purification was placed in a sealed tube with 16 ml. of concentrated ammonium hydroxide and shaken for a few minutes until a homogeneous solution was formed. After 20 hr. at room temperature the contents of the tube were distilled to yield 1.40 g. (24%) of V, b.p. 69–70° (8 mm.), plus 2.28 g. (45%) of the bis compound, VI, b.p. 180–192° (8–10 mm.).[13] Each was converted to the hydrochloride with ethanolic hydrogen chloride in quantitative yield. The salt of V consisted of glistening white platelets, m.p. 165–166°, while that from VI appeared as fine white needles, m.p. 149–150°. These m.p. values have been reported as 164° and 148°, respectively.[9] The specific activity of the hydrochloride of V was 0.46 μc. per mg., and of that from VI was 0.48 μc. per mg.

Reaction of N-(β-haloethyl)phthalimides with sodium or potassium cyanide. In a typical experiment 8 g. of N-(β-bromoethyl)-phthalimide, (III),[14] 2.6 g. of potassium cyanide, and 140 ml. of 80% ethanol were continuously stirred and refluxed for 24 hr. The clear red-brown solution was concentrated to dryness at reduced pressure and the residue was extracted with boiling dioxane. The residue from evaporation of the dioxane extract was crystallized from water to give 2.6 g. of large plates, m.p. 125–126°. A recrystallized sample, m.p. 127–129°, proved to be identical with N-(β-hydroxyethyl)phthalimide, (II).[14] No other definite product could be isolated.

A repetition of this experiment using N,N-dimethylformamide as the solvent in place of 80% ethanol gave an 11% yield of impure N-(β-cyanoethyl)phthalimide, (IV), m.p. 139–144°, (pure IV melts at 151–152°). Extending the reaction time to 70 hr. at 120–130° gave no better results. When the procedure of Sakami *et al*[15] involving the use of acetone-free methanol as solvent was tried, unchanged III was recovered. When N-(β-chloroethyl)phthalimide[16] was refluxed with sodium cyanide in 50% ethanol, the mixture darkened rapidly and no definite product could be isolated. Reaction of N-(β-iodoethyl)phthalimide[17] with potassium cyanide in 95% ethanol gave II as the only product.

College of Agriculture
University of Wisconsin
Madison 6, Wis.

(9) A. P. Terent'ev, K. I. Chursina, and A. N. Kost, *J. Gen. Chem.*, (*USSR*) **20**, 1073 (1950).

(10) The authors wish to thank Mr. Michael Bach for making this measurement.

(11) J. A. McCarter, *J. Am. Chem. Soc.*, **73**, 483 (1951).

(12) C. H. G. Hands and B. Y. Walker, *J. Soc. Chem. Ind.*, 67, 458 (1948).

(13) S. R. Buc, *Org. Syntheses*, **27**, 3 (1947).

(14) T. O. Soine, *J. Am. Pharm. Assoc.*, **33**, 141 (1944).

(15) W. Sakami, W. E. Evans, and S. Gurin, *J. Am. Chem. Soc.*, 69, 1110 (1947).

(16) H. Wenker, *J. Am. Chem. Soc.*, **59**, 422 (1937).

(17) E. E. Blaise, and A. Cornillot, *Compt. rend.*, **178**, 1186 (1924).

Anomalous Hofmann Elimination Reactions

M. A. Thorold Rogers

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Weinstock[1] questions the conclusion of Ingold and Rogers[2] and in particular suggests that the alleged new *cis-trans* isomer, m.p. 107–8°, of the previously described α-benzylcrotonic acid (m.p. 99°) which these authors describe, is, in fact, 1-benzylcyclopropanecarboxylic acid. Such a possibility was considered by Rogers[3] and rejected for two reasons: the absorption of more hydrogen (3.25 atoms) on catalytic reduction in aqueous solution over Adam's platinum oxide catalyst than was required for full hydrogenation of the benzene ring system; and the isolation,[2] following ozonolysis in chloroform at 0° for 2 hr., of acetaldehyde as its 2,4-dinitrophenylhydrazone, m.p. 154°, raised on admixture with authentic material of m.p. 163°, and depressed by mixture with the dinitrophenylhydrazone of formaldehyde.

Small samples of both isomers being available, it has been possible to decide the point in the light of modern spectroscopic knowledge. The infrared absorption of the alleged isomer m.p. 107° not only differs greatly from that of the isomer m.p. 99°, but shows the peak at 9.70 μ, already recorded for 1-benzylcyclopropanecarboxylic acid by Piehl and Brown,[4] which Slabey[5] has shown to be charac-

(1) Weinstock, *J. Org. Chem.*, **21**, 540 (1956).

(2) Ingold and Rogers, *J. Chem. Soc.*, 722 (1935).

(3) Rogers, Thesis "The mechanism of the reduction of unsaturated organic compounds," London, 1934, pp. 40 & 79.

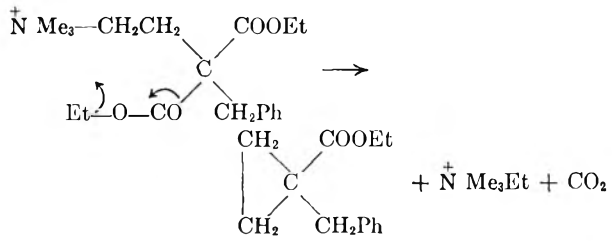
(4) Piehl and Brown, *J. Am. Chem. Soc.*, **75**, 5026 (1953).

(5) Slabey, *J. Am. Chem. Soc.*, **76**, 3605 (1954).

teristic of 1,1-disubstituted cyclopropanes; all six peaks recorded by the former authors are present, with maximum deviation of $\pm 0.1\ \mu$.

Ultraviolet absorption also confirms the supposition of Weinstock. Both compounds show a weak maximum at 260 mμ, but in the case of α-benzylcrotonic acid (m.p. 99°) only there is very considerable overlapping end absorption due to the conjugated carboxylic acid system.

Despite the unexplained results of the ozonolysis experiment, these observations confirm Weinstock's assertion that there is no evidence that the thermal degradation of 3,3-dicarboethoxy-4-phenylbutyltrimethylammonium iodide or ethoxide proceeds by a Wagner-Meerwein rearrangement. But rather than formulate the mechanism as Weinstock has done, it is preferred to represent it as an intramolecular 1,3 elimination process:



According to this one would not expect a 4,4-dicarboethoxybutyl quaternary ammonium salt to give cyclobutane derivatives on thermal decomposition under non-hydrolytic conditions, whereas in Weinstock's formulation it would be just as probable as in the case of the lower homolog. Furthermore the special function of the carboethoxy group explains why in this example and the closely related one[6] which Weinstock quotes, cyclopropane derivatives are formed so readily while 3-phenylpropyltrimethylammonium hydroxide reacts normally.

These results do not substantially weaken the argument of Ingold and Rogers[7] in support of the views of Burton and Ingold on the mechanism of reduction by sodium amalgam.

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52 Styal Road
Wilmslow, Cheshire
England

(6) Rinderknecht and Niemann, *J. Am. Chem. Soc.*, **73**, 4259 (1951).

(7) Ingold and Rogers, *J. Chem. Soc.*, 717 (1935).

Communications TO THE EDITOR

Structure of Amphenone B and Related Amphenones

Sir:

Due to increased interest in Amphenone B[1] after its initial synthesis by Allen and Corwin,[2] further chemical studies seemed to be in order. One of the main purposes was to find new potential routes to the synthesis of amphenone-like compounds.

Originally the symmetrical glycol (I) was submitted to a pinacol-pinacolone rearrangement. The pinacolone formula (II) was assigned to Amphenone B by Allen and Corwin based on the results of a rather drastic alkali fission of its *N,N'*-tetramethyl derivative and an apparent negative iodoform test.[2] The course of the rearrangement in favor of this pinacolone (II) seemed to be in agreement with the findings of previous investigators[3] who demonstrated that generally in a symmetrical pinacol it is the strongest electron donating moiety which will migrate. Thus, in this particular instance, the methyl group being the only electron donator in the glycol (I) would migrate in preference to the benzene ring if its substituent existed as a *p*-ammonium ion.

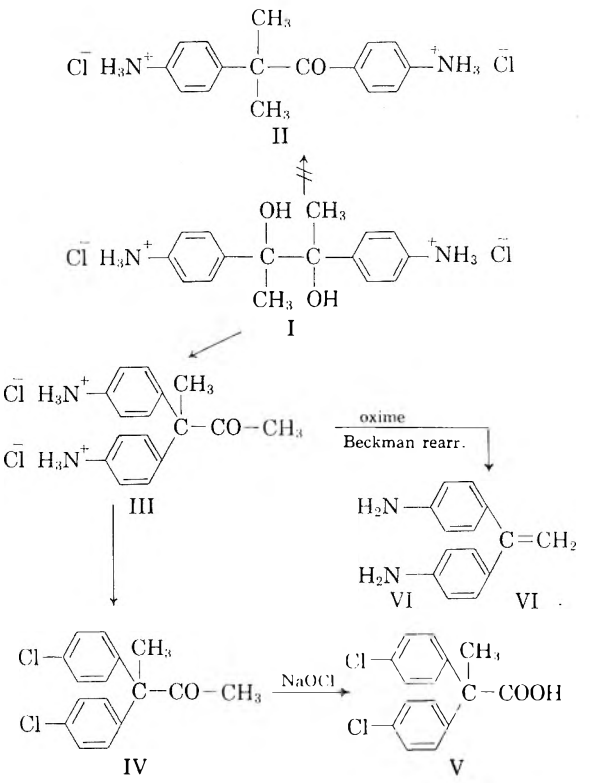
In a recent review[4] it has been stated that the pinacol-pinacolone rearrangement of symmetrical glycols seems to be far more complicated than anticipated previously and in view of these facts the question arose whether Amphenone B was to be formulated as (II) or could possibly have structure (III). The correctness of the latter formulation was proved by the following experiments.

Replacement of the amino groups of Amphenone B (III) by chlorine resulted in the ketone (IV) (73%, m.p. 58–60°) which was found to be identical to 3,3-bis(*p*-chlorophenyl)butanone-2[5] as indicated by mixed melting point and infrared spectra. Oxidation of ketone (IV) also yielded α,α-bis(*p*-chlorophenyl)propionic acid (m.p. 160–161°).[5]

The oxime of Amphenone B (90%, m.p. 220–222°, calcd. for $C_{16}H_{19}N_3O$: C, 71.35; H, 7.12; N, 15.62. Found: C, 71.07; H, 7.11; N, 15.47). was subjected to a Beckmann rearrangement by heating it in polyphosphoric acid to 120° for 15 minutes. The product isolated was identified as 1,1-bis(*p*-aminophenyl)ethylene (VI) (70%, m.p. 170–172°, calcd. for $C_{14}H_{14}N_2$: C, 79.96; H, 6.71; N, 13.32. Found: C, 80.03; H, 6.69; N, 13.61).

A similar course of the Beckmann rearrangement followed by deamination was observed by Price and Mueller[6] who obtained 1,1-dianisylethylene from the oxime of 3,3-dianisyl-2-butanone. The structure of compound VI is also supported by the infrared absorption bands: 890 cm.$^{-1}$ (>C=CH$_2$), 1620 cm.$^{-1}$ (C=C) and 833 cm.$^{-1}$ (*p*-disubstituted benzene).

The amino groups of VI were exchanged for chlorine via diazotation. The resulting 1,1-bis(*p*-chlorophenyl)ethylene showed a melting point of 84–85° (reported 84.6–85.8)[7] and the same ultraviolet absorption spectrum as found by Grummitt, Marsh, and Stearns.[8]



(1) M. J. Allen, R. Hertz, and W. W. Tullher, *Proc. Soc. Exptl. Biol. Med.*, **74**, 632 (1950); R. Hertz, M. J. Allen, and W. W. Tullner, *Proc. Soc. Exptl. Biol. Med.*, **75**, 627 (1950); **79**, 42 (1952); R. Hertz, W. W. Tullner, J. A. Schricker, F. G. Dhyse, and L. F. Hallman, *Recent Progr. in Hormone Research*, **11**, 119 (1955); A. E. Renold, *et al.*, *N. Engl. J. Med.*, **256**, 16 (1957).

(2) M. J. Allen and A. H. Corwin, *J. Am. Chem. Soc.*, **72**, 117 (1950).

(3) W. E. Bachmann and H. R. Steinberger, *J. Am. Chem. Soc.*, **56**, 170 (1934).

(4) D. J. Cram, in *Steric Effects in Organic Chemistry*, M. S. Newman, Editor, John Wiley and Sons, New York, 1956, 249–303.

(5) W. Voegtle and P. Laeuger, *Helv. Chim. Acta*, **38**, 46 (1955).

(6) C. C. Price and G. P. Mueller, *J. Am. Chem. Soc.*, **66**, 634 (1944).

(7) M. S. Newman and N. C. Deno, *J. Am. Chem. Soc.*, **73**, 3644 (1951).

(8) O. Grummitt, D. Marsh, and J. A. Stearns, *Anal. Chem.*, **24**, 702 (1952).

The structure of Amphenone B as being (III) was also indicated by the fact that an iodoform reaction yielded 20–25% iodoform as determined spectrophotometrically.[9] The ultraviolet spectrum of Amphenone B showed the absence of a benzoyl-type carbonyl group.

A comparison of the ultraviolet spectra of the pinacolones obtained by rearrangement of 3,4-bis-(*p*-aminophenyl)-3,4-hexanediol[2] and 2,3-bis-*p*-dimethylaminophenyl)-2,3-butanediol[10] indicate these pinacolones to be 4,4-bis(*p*-aminophenyl)-hexanone-3 and 3,3-bis(*p*-dimethylaminophenyl)-butanone-2.

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RESEARCH DEPARTMENT W. L. BENCZE
CIBA PHARMACEUTICAL PRODUCTS INC. M. J. ALLEN
SUMMIT, N. J.

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(9) S. D. Nogare, T. O. Norris, and J. Mitchell, Jr., *Anal. Chem.*, **23**, 1473 (1951).
(10) M. J. Allen, *J. Chem. Soc.*, 1598 (1951).

(−)-Menthoxyacetic Esters of the *Cis* and *Trans* Forms of *Meso*-3,4-diphenylcyclopentanol

Sir:

We wish to report the synthesis of the (−)-menthoxyacetic esters of the *cis* and *trans* forms of *meso*-3,4-diphenylcyclopentanol. The *cis* form was prepared by the reaction of the *cis* form of *meso*-3,4-diphenylcyclopentanol[1] with (−)-menthoxyacetyl chloride in pyridine. After purification by chromatographic adsorption and repeated crystallization from 95% ethanol and from *n*-pentane, it melted at 66.5–67.0°; $[\alpha]_D^{25}$ − 49.3° ± 0.2°, c = 0.035 g. per cc. in methyl ethyl ketone.

Anal. Calcd. for $C_{29}H_{38}O_3$: C, 80.14; H, 8.81. Found: C, 80.10, 80.29; H, 8.80, 8.85.

The *trans* form was prepared by the reaction of the *p*-toluenesulfonyl ester of the *cis* alcohol with the sodium salt of (−)-menthoxyacetic acid. After exhaustive purification it melted at 76.5–77.0°; $[\alpha]_D^{25}$ − 55.1° ± 0.2°, c = 0.035 g. per cc. in methyl ethyl ketone.

Anal. Calcd. for $C_{29}H_{38}O_3$: C, 80.14; H, 8.81. Found: C, 80.14, 80.19; H, 8.86, 8.75.

The difference of 5.8° in the rotation of the *cis* and *trans* forms of the menthyl esters confirms the view that diastereoisomers of this type may be expected to differ in optical rotation.[2]

DEPARTMENT OF CHEMISTRY R. J. HORVAT
STANFORD UNIVERSITY C. R. NOLLER
STANFORD, CALIF.

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(1) H. Burton and C. W. Shoppee, *J. Chem. Soc.*, 570 (1939).
(2) C. R. Noller, *Science*, **105**, 546 (1947).