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Benzflavothebaone[1]

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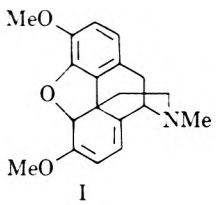
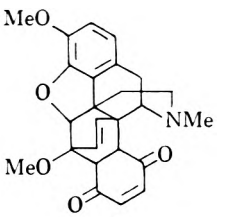
Received January 13, 1958

The Diels-Alder adduct from thebaine and 1,4-naphthaquinone has been shown to undergo most of the reactions given by thebainequinol. The acid rearrangement product, benzflavothebaone, which is analogous to flavothebaone, has been degraded to nitrogen-free products. Unlike flavothebaone it is very easily converted into a quinone.

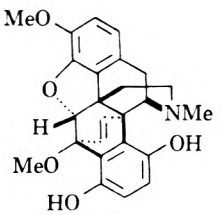
Diels-Alder adducts between thebaine (I) and several dienophiles have been reported[2-4] and the stereochemistry of the *p*-benzoquinone adduct has been examined fully by Schöpf, von Gottberg, and Petri.[3] Sandermann, who first reported the *p*-benzoquinone adduct (II),[2] observed that it underwent conversion into thebainequinol (III) on prolonged heating in ethanol, a change very easily effected in the presence of acetic acid.[3] The acid rearrangement of thebainequinol affords flavothebaone for which the structure (IV) has recently been established.[5,6] The 1,4-naphthaquinone adduct of thebaine would be expected to show similar behavior, and its reactions have in fact been found to be parallel to those of thebainequinol.



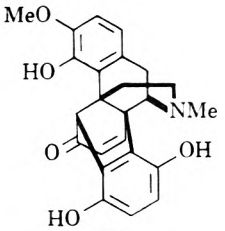
I



II

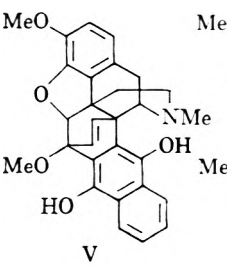


III

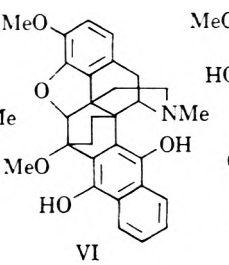


IV

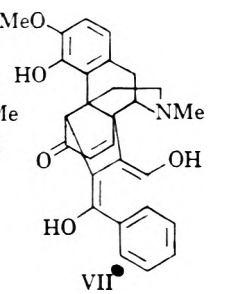
The adduct itself was sensitive to air and readily decomposed to tars, and the product m.p. 240° described by Sandermann[2] was very probably the isomerized base, thebaine-1,4-naphthaquinol (V) which is quite stable; a different crystalline modification m.p. 267° was obtained by us. It resembles thebainequinol in forming a monoacetyl derivative and a monomethyl ether which could not be quaternized at the *N*-atom with methyl iodide or methyl sulfate owing to the steric hindrance at the *N*-atom by one of the OH-groups. In this respect the base resembles thebainequinol; conversion of thebainequinol to flavothebaone (IV) results in the movement of the aromatic nucleus in space



V



VI



VII

(1) A preliminary report of this work has already been published; K. W. Bentley, J. C. Ball, and H. M. E. Cardwell, *Chem and Ind. (London)*, 1483 (1956).

(2) W. Sandermann, *Ber.*, **71**, 648 (1938).

(3) C. Schöpf, K. von Gottberg, and W. Petri, *Ann.*, **536**, 216 (1938).

(4) K. W. Bentley and A. F. Thomas, *J. Chem. Soc.*, 1863 (1956).

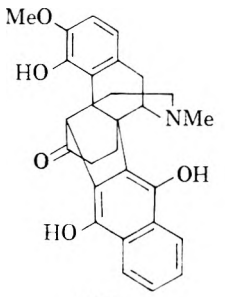
(5) K. W. Bentley, J. Dominguez, and J. P. Ringe, *Chem. and Ind. (London)*, 1353 (1956); *J. Org. Chem.*, **21**, 1348 (1956); **22**, 409, 418, 422, 424, 599 (1957).

(6) J. Meinwald and G. A. Wiley, *Chem. and Ind. (London)*, 957 (1956); *J. Am. Chem. Soc.*, **79**, 2569 (1957).

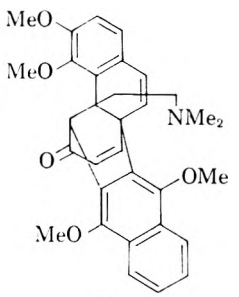
sufficiently far away from the nitrogen atom for quaternization to be possible in the rearranged series. Catalytic reduction readily afforded dihydrothebaine-1,4-naphthaquinol (VI).

When treated with concentrated hydrochloric acid in glacial acetic acid at 100° for 6 hours, thebaine-1,4-naphthaquinol afforded the hydrated hydrochloride of benzflavothebaone (VII), $C_{28}H_{25}O_5N\cdot HCl\cdot 2H_2O$. Benzflavothebaone dissolved in aqueous alkalis to give a deep purple-red solution, different in color from that of flavothebaone, and very sensitive to air oxidation, the color being discharged rapidly in air. The monomethyl ether of thebaine-1,4-naphthaquinol, obtained by treatment of the base with hot methyl sulfate or with hot methyl *p*-toluenesulfonate, was rearranged to the monomethyl ether of benzflavothebaone. The latter was soluble in alkalis to give a yellow solution which was stable in air. Dihydrobenzflavothebaone (VIII) was obtained by acid rearrangement of dihydrothebaine-1,4-naphthaquinol and also by sodium amalgam-reduction of benzflavothebaone. In alkalis, dihydrobenzflavothebaone was rapidly oxidised on shaking in air.

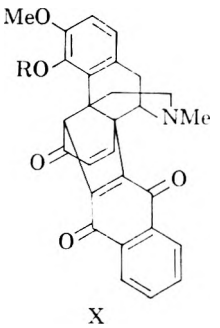
Triacetylbenzflavothebaone and benzflavothebaone trimethyl ether methiodide have been prepared. The latter was readily degraded in hot alkali to the methine base (IX) which was more conveniently obtained from benzflavothebaone without isolation of the intermediate quaternary salt. Under the same conditions dihydrobenzflavothebaone afforded the dihydromethine.



VIII

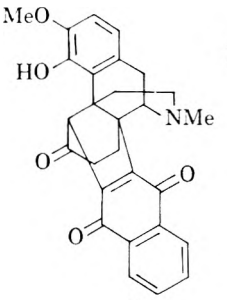


IX

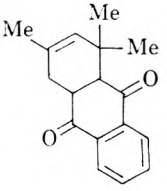


X

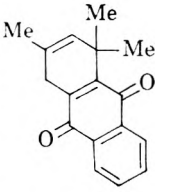
Oxidation of benzflavothebaone by air in dilute alkalis gave benzflavothebaone-quinone (X, R = H). This gave a monoacetyl derivative (X, R = CH_3CO) in poor yield and could not be successfully converted into the methiodide for degradative studies. The quinone absorbed two moles of hydrogen on catalytic reduction affording dihydrobenzflavothebaone (VIII) whereas reduction with sulfurous acid gave benzflavothebaone. Air oxidation of alkaline dihydrobenzflavothebaone afforded dihydrobenzflavothebaone-quinone (XI). In warm alcoholic alkali, benzflavothebaone-quinone gave a deep purple solution which faded on standing in air. Similar behavior has been described for the compound (XII) which Fieser and Wieghard[7] have prepared by Diels-Alder reaction of 1,1,3-trimethylbutadiene with 1,4-naphthaquinone; the adduct (XII) gave the quinone (XIII) on treatment with air in the presence of potassium hydroxide, and this quinone gave a blue-green solution in alcoholic potash, the color fading on shaking.



XI



XII



XIII

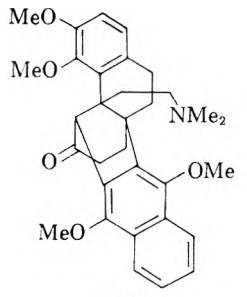
Catalytic reduction of the methine base afforded the tetrahydro compound (XIV). No success was obtained with Hofmann degradation of the methine but pyrolysis of the methine *N*-oxide[8] readily gave the neutral compound (XV) in quite good yield. The ultraviolet spectrum of the nitrogen-free substance was very similar to that of the methine base. Pyrolysis of the dihydromethine *N*-oxide and of the tetrahydromethine *N*-oxide afforded the neutral compounds XVI, and XVII respectively. The three nitrogen-free products XV, XVI, and XVII on hydrogenation gave the common product XVIII, $C_{30}H_{32}O_5$.

In the parent flavothebaone series, the methine base underwent rearrangement in hot ethanolic alkali to a non-isomeric base, the ψ-methine, in about 80% yield. This reaction has been attempted many times with benzflavothebaone methine but crystalline products have not been isolated. The neutral compound XV from the methine likewise gave non-crystalline products but the methine methiodide was converted, in very poor yield, into the ψ-methine methiodide (XIX), the ultraviolet spectrum of which closely resembled those of the crude materials from the alkali treatment of the methine base and of the nitrogen-free product (XV).

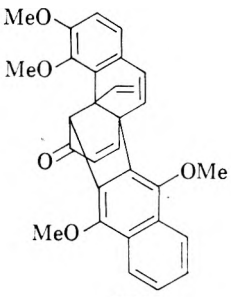
Mechanisms for the conversion of thebaine-1,4-naphthaquinol into benzflavothebaone and of

(7) L. F. Fieser and C. W. Wieghard, *J. Am. Chem. Soc.*, 62, 153 (1940).

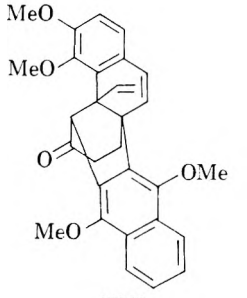
(8) K. W. Bentley, J. C. Ball, and J. P. Ringe, *J. Chem. Soc.*, 1963 (1956).



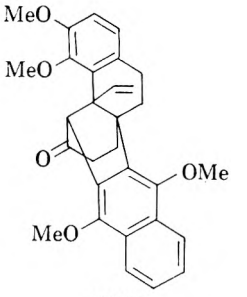
XIV



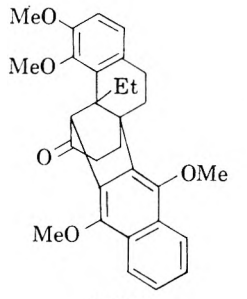
XV



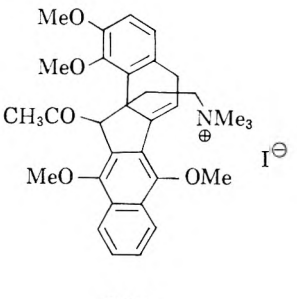
XVI



XVII



XVIII



XIX

the methine into the ψ-methine are essentially the same as those in the flavothebaone series and need no further elaboration. The structure of benzflavothebaone is assumed by analogy with that of flavothebaone; as the structure of the latter has now been established,[5] complete degradation of the neutral compound (XVIII) has not been attempted. Bromination afforded a tribromo derivative $C_{30}H_{29}O_5Br_3$, and hydroxylamine in alcoholic pyridine gave the oxime $C_{30}H_{33}O_5N$, which underwent Beckmann rearrangement to an isomeric compound.

EXPERIMENTAL

Unless otherwise stated, all ultraviolet spectra were measured in methanol solution.

Attempted preparation of thebaine-1,4-naphthaquinone. 1,4-Naphthaquinone (1.02 g.) dissolved in chloroform (10 ml.) was added to thebaine (2 g.) in chloroform (10 ml.); a distinct deepening in color was apparent. The solution was evaporated in a stream of air without heating and afforded a yellowish crystalline solid which, on becoming dry, turned black within a few seconds. On account of the sensitivity to air, recrystallization was never achieved. When the reaction was attempted in 2-ethoxyethanol, the only product to be isolated was thebaine-1,4-naphthaquinol, m.p. 267°. This proved to be the only clean crystalline material obtainable and was always formed after heating for some time in alcohol or more quickly in the higher-boiling 2-ethoxyethanol.

Thebaine-1,4-naphthaquinol. Thebaine (40 g.) was dissolved in hot 2-ethoxyethanol (200 ml.) and 1,4-naphthaquinone (20.4 g.) in hot 2-ethoxyethanol (100 ml.) was added. With pure 1,4-naphthaquinone a deepening in color was observed, but this was not noticeable with the usual samples, which contained dark impurities. On boiling for 10 min., the solution became darker in color but no solid matter separated, even on cooling. Glacial acetic acid (32 ml.) was added and the solution was heated under reflux for a further 10 min. Thebaine-1,4-naphthaquinol separated as white prisms on cooling, and these were washed with cold alcohol. The yield was 55 g., m.p. 267° (dec.), unchanged on recrystallization from 2-ethoxyethanol. (Sandermann[2] gave m.p. 239–240°). $[\alpha]_D^{21}$ +34° ± 2° ($CHCl_3$, *c*, 0.79). λ_{max}: 215; 250; 300; 335, and 350 mμ; ϵ_{max}: 47,860, 28,180; 4,169, 7,079, and 7,943.

Anal. Calcd. for $C_{29}H_{27}O_5N$: C, 74.2; H, 5.8. Found: C 74.3, H, 5.6.

Rapid crystallization from 2-ethoxyethanol or from alcohol gave granular prisms; slow crystallization from the same solvents gave slender rods as well. The base was sparingly soluble in alcohol and showed no tendency to dissolve in alkalis; no coupling with diazotized sulfanilic acid could be detected. No methiodide separated when a benzene solution containing methyl iodide was allowed to stand for 3 days. Concentrated sulfuric acid gave a very intense permanganate-color with the base.

The *hydrochloride* was obtained when the base was dissolved in alcoholic HCl and diluted with water as white rods, m.p. 215° dec.

Anal. Calcd. for $C_{29}H_{27}O_5N.HCl.H_2O$: C, 66.4; H, 5.8; Cl, 6.8. Found: C, 66.4; H, 6.1; Cl, 6.1.

When an alcoholic solution of the salt was boiled for a few minutes and then allowed to cool, hydrolysis occurred and the original base, m.p. 267°, was deposited. This behavior is parallel to that of thebaine quinol.

Monoacetylthebaine-1,4-naphthaquinol. Thebaine-1,4-naphthaquinol (1.0 g.) was dissolved in pyridine (10 ml.), acetic anhydride (5 ml.) added, the solution was allowed to stand at room temperature for 24 hr., and then evaporated *in vacuo* on a water bath. Dilute acetic acid was added, the solution was treated with sodium bicarbonate and the precipitated base was collected and crystallized from alcohol. Recrystallization from 2-ethoxyethanol gave *monoacetylthebaine-1,4-naphthaquinol* as colorless needles m.p. 267°, depressed to 240° on mixing with the starting material.

Anal. Calcd. for $C_{31}H_{29}O_6N$: C, 72.9; H, 5.7; (1) CH_3CO, 9.4. Found: C, 72.4; H, 5.6; CH_3CO, 9.3.

Thebaine-1,4-naphthaquinol monomethyl ether. Thebaine-1,4-naphthaquinol (2 g.) was dissolved in hot methyl sulfate (5 ml.), the solution cooled in ice and treated with ether (40 ml.) to remove excess of methyl sulfate, and the sticky precipitate collected. Trituration with a small quantity of ethanol gave a white product which was sparingly soluble in water but readily so in dilute acids. Recrystallization from 2-ethoxyethanol gave *thebaine-1,4-naphthaquinol monomethyl ether*, m.p. 252°, unchanged on further recrystallization. $[\alpha]_D^{20}$ −48° ± 1° ($CHCl_3$, c, 1.25).

Anal. Calcd. for $C_{30}H_{29}O_5N$: C, 74.5; H, 6.1, active H, 0.21. Found: C, 74.3; H, 6.2; active H, 0.25.

The same product was obtained by methylation with methyl *p*-toluenesulfonate following the directions of Schöpf *et al.*[3] for the methylation of flavothebaone.

Dihydrothebaine-1,4-naphthaquinol. Thebaine-1,4-naphthaquinol (3.0 g.) dissolved in glacial acetic acid (40 ml.) was shaken under hydrogen with platinum oxide (0.1 g.). One mole of hydrogen was absorbed in 30 min. at 18°. The solution was filtered (kieselguhr), diluted with water, treated with ammonia solution, and the product collected and crystallized from alcohol when *dihydrothebaine-1,4-naphthaquinol* was obtained as orange needles, m.p. 266°. $[\alpha]_D^{21}$ 0° ± 1° λ_{max}: 215; 253; 290; 330, and 343 mμ; ϵ_{max}: 79,430; 47,860; 3,981; 7,950, and 8,320.

Anal. Calcd. for $C_{29}H_{29}O_5N$: C, 74.0; H, 6.2. Found: C, 74.0; H, 6.2.

The *hydrochloride* was obtained as glistening plates, m.p. 210–212°, sintering at 205°, from dilute hydrochloric acid.

Anal. Calcd. for $C_{29}H_{29}O_5N \cdot HCl \cdot H_2O$: C, 66.2; H, 5.8; Cl, 6.8. Found: C, 66.7; H, 5.8; Cl, 7.0.

Benzflavothebaone hydrochloride. Thebaine-1,4-naphthaquinol (40 g.) was dissolved in hot glacial acetic acid (120 ml.) and concentrated hydrochloric acid (120 ml.) was added. A crystalline salt began to separate after 20 min. under reflux; heating was continued for 4 hr. on a steam bath. Hot water (250 ml.) was added and, after cooling, the product was collected and dried in air, when 36.5 g. of *benzflavothebaone hydrochloride* was obtained as yellow plates, m.p. 264° (dec.). Recrystallization in bulk was found to be inconvenient, but for analysis it was achieved by adding concentrated HCl to an alcoholic solution of the salt. $[\alpha]_D^{21}$ +434° ± 4° (EtOH, c, 0.36).

Anal. Calcd. for $C_{28}H_{25}O_5N \cdot HCl \cdot 2H_2O$: C, 63.6; H, 5.7; Cl, 6.7. Found after drying at 140° *in vacuo:* C, 63.5; H, 5.8; Cl, 7.5. Loss in weight of air-dried salt on heating at 140° *in vacuo:* Calcd. for loss of HCl from $C_{28}H_{25}O_5N \cdot 2HCl \cdot 2H_2O$:[9] 6.5. Found: 6.6, 7.1.

An intense red solution was obtained on dissolving the salt in concentrated sulfuric acid. In alkalis an exceedingly intense purple-red solution was obtained and, on shaking, the color was discharged. Positive diazo-coupling occurred with the alkaline solutions both before and after air oxidation. Ultraviolet spectrum: λ_{max}: 235; 250 (inflection); 288, and 385 mμ. ϵ_{max}: 44,670; 26,300; 7,586, and 4,266. Spectrum in aq. 2*N* NaOH with dithionite antioxidant: 7,586, and 4,266. Spectrum in aq. 2*N* NaOH with dithionite antioxidant: λ_{max}: 510 mμ ϵ_{max}: 3,981.

Benzflavothebaone monomethyl ether hydrochloride. Thebaine-1,4-naphthaquinol monomethyl ether (178 mg.) was dissolved in glacial acetic acid (2 ml.), concentrated HCl (3 ml.) was added and the solution was heated under reflux for 1 hr. After concentration to 2 ml. the solution was treated with more concentrated HCl (3 ml.) and the precipitated salt (106 mg.) was collected and recrystallized from dilute acetic acid, m.p. 255–260° (dec.) $[\alpha]_D^{20}$ +301° ± 1° (EtOH, *c*, 0.87).

Ultraviolet spectrum in 2*N* NaOH: λ_{max}: 420 mμ ϵ_{max}: 3,981.

Anal. Calcd. for $C_{29}H_{27}O_5N \cdot HCl \cdot 2H_2O$: C, 64.2; H, 5.6; Cl, 6.6; active-H, 1.1. Found after drying at 140° *in vacuo:* C, 63.7; H, 5.8; Cl, 6.3; active-H, 1.2.

In aqueous sodium hydroxide a yellow solution was obtained which was unaffected on shaking in air. Diazotized sulfanilic acid gave an intense red solution in alkalis; concentrated sulfuric acid gave a crimson color.

Dihydrobenzflavothebaone hydrochloride. When treated with concentrated hydrochloric acid and glacial acetic acid in the manner outlined for the rearrangement of thebaine-1,4-naphthaquinol to benzflavothebaone hydrochloride the dihydro compound behaved in a similar way, depositing the almost-white dihydrobenzflavothebaone hydrochloride as the hydrated salt in almost quantitative yield. M.p. 280–290°. $[\alpha]_D^{22}$ +152° ± 3° (EtOH, *c*, 0.49), λ_{max}: 247; 286, and 335 mμ. ϵ_{max}: 33,110; 6,026, and 5,012.

Anal. Calcd. for $C_{29}H_{27}O_5N \cdot HCl \cdot 2H_2O$: C, 63.4; H, 6.1; Cl, 6.7. Found after drying at 140° *in vacuo:* C, 63.0; H, 5.8; Cl, 6.9.

In concentrated sulfuric acid a moderately intense green color resulted. Aqueous alkali gave a bright red solution, the color being discharged on shaking in air. Both the initial alkali-solution and the air-oxidized one gave deep red colors on addition of diazotized sulfanilic acid.

Reduction of benzflavothebaone with sodium amalgam. Benzflavothebaone hydrochloride (1.0 g.) was dissolved in hot alcohol (25 ml.) and sodium amalgam (0.5 g. Na in 30 g. Hg) added. The color remained yellow for several minutes and then on warming became red-brown, and after a short time an orange solid began to separate. When most of the amalgam had reacted, concentrated hydrochloric acid was added dropwise; the color of the solution changed sharply to green and addition of more HCl gave a precipitate which was collected and recrystallized from water (100 ml.) to which concentrated hydrochloric acid was added. Dihydrobenzflavothebaone hydrochloride was obtained as very pale yellow plates. M.p. 280–290°. $[\alpha]_D^{22}$ +148° ± 3° (EtOH *c*, 0.45), λ_{max} and ϵ_{max} the same as for dihydrobenzflavothebaone. The reduction product gave the same alkali- and concentrated sulfuric acid colors as the material from the rearrangement of dihydrothebaine-1,4-naphthaquinol.

Triacetylbenzflavothebaone. Benzflavothebaone hydrochloride (2 g.) was dissolved in hot acetic anhydride (10 ml.) and pyridine (3 ml.) was added to the clear solution which was then boiled for 1 hr. The mixture was then diluted with water (100 ml.) and decomposed with sodium carbonate, and the product was collected. Three recrystallizations from alcohol gave *triacetylbenzflavothebaone* as colorless needles, m.p. 258–260°. $[\alpha]_D^{20}$ +237° + 2° ($CHCl_3$, *c*, 0.59). λ_{max}: 215; 230; 280, and 340 mμ. ϵ_{max}: 60,260; 60,250; 16,980, and 2,239.

Anal. Calcd. for $C_{34}H_{31}O_8N$: C, 70.2; H, 5.4; (3) CH_3CO, 22.2. Found: C, 69.9; H, 5.4; CH_3CO, 20.7.

Benzflavothebaone trimethyl ether methiodide. The air in a flask containing a suspension of benzflavothebaone hydrochloride (20 g.) in methyl sulfate (68 ml.) was expelled with hydrogen and a solution of sodium hydroxide (25 g.) in boiled water (75 ml.) added slowly so that the reaction temperature was kept around 40° (mechanical stirring). After the addition, the temperature was raised to 60–70° to decompose the excess of methyl sulfate, and hot water (100 ml.) followed by an excess of aqueous potassium iodide was added. The solution was heated to the boiling point, treated with charcoal, filtered, and the minutely crystalline product collected from the cold filtrate. *Benzflavothebaone trimethyl ether methiodide*, m.p. 198–200° (dec.), was thus obtained, m.p. unchanged on recrystallization from water. $[\alpha]_D^{21}$ +244° ± 2° ($CHCl_3$, *c*, 0.72).

Anal. Calcd. for $C_{32}H_{34}O_5NI \cdot 2H_2O$: C, 56.9; H, 5.7; I, 18.8. Found after drying at 140° *in vacuo:* C, 56.7, 56.8; H, 5.6 5.8; I, 19.2.

Benzflavothebaone trimethyl ether methine. Treatment of benzflavothebaone trimethyl ether methiodide with hot aqueous alkali readily converted it into the methine. The alternative method below obviates the need to prepare the intermediate methiodide, and affords a higher overall yield.

Benzflavothebaone hydrochloride (40 g.) was covered with methyl sulfate (136 ml.) contained in a 1-l. flask with a sealed-in stirrer. The air was displaced by means of hydrogen and NaOH (50 g.) in boiled water (150 ml.) was added slowly so as to maintain the reaction temperature at 40°. (Strong cooling delays the reaction which subsequently gets out of control.) The reaction mixture was heated to 80–90° to decompose excess of methyl sulfate, and then poured into hot water (1 l.). Sodium hydroxide was added until the mixture was alkaline to litmus, followed by more NaOH (50 g.) dissolved in a little water (rapid stirring was desirable at this stage). Separation of the methine began at once, and after 15 min. at 95° the aqueous phase was removed by decantation and the solids washed well with water. Recrystallization from alcohol (200 ml.) (charcoal treatment) gave 36 g. of *benzflavothebaone trimethyl ether methine* as colorless prisms, m.p. 199°. $[\alpha]_D^{24}$ −21° ± 2° ($CHCl_3$, *c*, 0.70). λ_{max}: 233; 280, and 345 mμ ϵ_{max}: 63,100; 23,400, and 22,910.

(9) Flavothebaone also forms a dihydrochloride. These salts are only stable in the presence of excess of hydrochloric acid, and slowly lose hydrogen chloride on drying in the air. These salts are believed to be formed by protonation of the system O=C—C=C—Ar to $HO{=}C{-}C{=}C{-}Ar^{+}$. The dihydrochlorides are noticeably different in color from the monohydrochlorides, see ref. 5, paper 4.

Anal. Calcd. for $C_{32}H_{33}O_6N$: C, 75.2; H, 6.5. Found: C, 74.9; H, 6.5%.

The *methiodide* was obtained when a slight excess of methyl iodide was added to a solution of the methine in benzene; after a few minutes the solution became turbid and deposited a granular solid. Recrystallization from water gave yellow needles, m.p. 244°. $[\alpha]_D^{24}$ −14° ± 1° ($CHCl_3$, *c*. 1.78).

Anal. Calcd. for $C_{33}H_{36}O_5NI \cdot H_2O$: C, 59.1; H, 5.7; I, 18.9. Found: C, 59.1; H, 5.8; I, 19.4.

The *picrate*, prepared in and recrystallized from alcohol, was obtained as yellow prisms, m.p. 232°.

Anal. Calcd. for $C_{38}H_{36}O_{12}N_4$: C, 61.6; H, 4.9; N, 7.6. Found: C, 61.9; H, 4.8; N, 7.9.

Benzflavothebaone quinone. Air was bubbled into a solution of benzflavothebaone hydrochloride (2 g.) in water (100 ml.) containing 0.880 of ammonia solution (40 ml.) and covered with a layer of benzene (100 ml.), until the aqueous phase became colorless and the benzene phase a clear orange. The benzene phase was separated, dried with sodium sulfate (short drying, as the product tended to crystallize), and evaporated when *benzflavothebaone quinone* was obtained as a dark orange crystalline solid (1.25 g.) m.p. 269°, raised to 278° on recrystallization from 2-ethoxyethanol, $[\alpha]_D^{20}$ +220° ± 40° ($CHCl_3$, c, 0.67). λ_{max}: 215; 250 (inflection); 290 (inflection); 335; 410 (inflection) mμ. ϵ_{max}: 21,880; 15,850; 6,760; 3,310, and 310.

Anal. Calcd. for $C_{28}H_{23}O_5N$: C, 74.1; H, 5.1; N, 3.1. Found: C, 73.9; H, 5.1; N, 2.9.

The melting point was variable (278° highest recorded) and mere recrystallization from alcohol or aqueous 2-ethoxyethanol gave a material paler in color and of lower melting point (down to 265°). The use of sodium hydroxide in place of ammonia gave the same compound but in about one third the yield. A solution of the quinone in dilute acid was treated with excess alkali and warmed; this caused the solution to become deep purple (like benzflavothebaone in alkali), the color being discharged on shaking.

Acetylbenzflavothebaone quinone. A solution of benzflavothebaone quinone (650 mg.) in acetic anhydride (8 ml.) and pyridine (2 ml.) was heated under reflux for one hour and the resulting red solution diluted with water and decomposed with sodium carbonate. The acetyl compound was collected and crystallized from alcohol (20 ml.) to give 180 mg. of deep orange needles, m.p. 234–235°.

Anal. Calcd. for $C_{30}H_{25}O_6N \cdot {}^1/_2H_2O$: C, 71.4; H, 5.2. Found: C, 71.4; H, 5.3.

Catalytic reduction of benzflavothebaone quinone. The quinone (1.0 g.) in glacial acetic acid (20 ml.) with platinum oxide (0.05 g.) was shaken under hydrogen at 19°. Absorption ceased after 2 hr. when 2 moles had been absorbed. Warm concentrated hydrochloric acid was added and the solution was cooled. Brownish needles separated (0.61 g.). This product was recrystallized from alcohol with the addition of concentrated hydrochloric acid to yield pale orange-yellow plates, m.p. 280–290°. The ultraviolet and infrared spectra were the same as those of dihydrobenzflavothebaone; colors with concentrated sulfuric acid and with alkalis were the same as those of dihydrobenzflavothebaone.

Reduction of benzflavothebaone quinone with sulfurous acid. When sulfur dioxide was bubbled into an aqueous alcoholic hydrochloric acid solution of the quinone the color of the solution changed from orange to yellow-orange within about 5 min. The resulting solution was concentrated by boiling and treated with concentrated hydrochloric acid and the resulting crystalline solid was collected, m.p. 260–270°. $[\alpha]_D^{21}$ +433° ± 2° (EtOH, *c*, 0.58). λ_{max}: 235; 250 (inflection); 290; 370 mμ: ϵ_{max}: 42,660; 25,120; 6,918; 3,981.

Acetylation of this material gave a product m.p. 248°, unchanged on further recrystallization, which did not depress the melting point of authentic triacetylbenzflavothebaone, and had the same ultraviolet spectrum as this compound.

Air oxidation of dihydrobenzflavothebaone. Under the conditions already outlined for the air oxidation of benzflavothebaone to the quinone, the dihydro compound (2 g.) afforded a *dihydrobenzflavothebaone quinone* (1.4 g.) which like the quinone had a rather variable melting point. Colors in concentrated sulfuric acid and in alkalis were like those of the quinone but the ultraviolet spectrum did show a definite difference. λ_{max}: 253; 280 (inflection); 330. mμ. ϵ_{max}: 19,950; 8,913; 3,715.

Anal. Calcd. for $C_{28}H_{25}O_5N$: C, 73.8; H, 5.5. Found: C, 74.1; H, 5.6.

Dihydrobenzflavothebaone trimethyl ether dihydromethine. The methine base readily absorbed 2 moles of hydrogen on catalytic reduction over platinum oxide in acetic acid solution at 20°. *Dihydrobenzflavothebaone trimethyl ether dihydromethine* was obtained as needles, m.p. 171°, from methanol. $[\alpha]_D^{18}$ +154° ± 2° ($CHCl_3$, *c*, 0.80). λ_{max}: 239, 290 mμ. ϵ_{max}: 69,180; 8,913.

Anal. Calcd. for $C_{32}H_{37}O_5N$: C, 74.6; H, 7.2. Found: C, 74.3; H, 7.3.

The *methiodide* was obtained after 30 min. when methyl iodide was added to a benzene solution of the base. It was obtained as colorless needles, m.p. 262°, on recrystallization from water.

Anal. Calcd. for $C_{33}H_{40}O_5NI \cdot 2H_2O$: C, 58.8; H, 6.3; I, 18.9. Found: C, 58.7; H, 6.3; I, 18.8.

Benzflavothebaone trimethyl ether methine N-oxide perchlorate. The methine (1 g.) was treated with 30% hydrogen peroxide (5 ml.) on a steam bath for 1 hr. during which time an orange oil and a watery aqueous phase were produced. The volatile materials were removed *in vacuo* and the crude *N*-oxide was dissolved in dilute hydrochloric acid. Addition of aqueous sodium perchlorate gave a white gel which crystallized on shaking. Two recrystallizations from aqueous alcohol gave the *perchlorate* as white needles, m.p. 181°.

Anal. Calcd. for $C_{32}H_{34}O_{10}NCl \cdot H_2O$: C, 59.4; H, 5.6. Found: C, 59.0; 59.4; H, 5.5, 5.6.

Benzflavothebaone trimethyl ether desazamethine. The methine (15 g.) and 30% hydrogen peroxide (45 ml.) in a 250 ml. flask were heated for 40 min. on a steam bath and evaporated to dryness at 15 mm. When heated under 15 mm. pressure, decomposition occurred around 150–160° (bath temperature) over about 30 min. Purification of the crude material was achieved by crystallization from acetic acid followed by chromatography of the benzene-soluble materials. In this way 6.1 g. of *benzflavothebaone trimethyl ether desazamethine* m.p. 244°, sintering at 230° was obtained. $[\alpha]_D^{21}$ +49° ± 1° ($CHCl_3$, *c*, 2.12). λ_{max}: 237; 283; 344 mμ. ϵ_{max}: 74,130; 25,120; 3,311.

Anal. Calcd. for $C_{30}H_{26}O_5$: C, 77.2; H, 5.6. Found: C, 76.8; H, 5.6.

The compound was completely insoluble in acids and in alkalis but did dissolve in organic solvents.

Catalytic reduction. Reduction was rather slow in acetic acid solution in the presence of platinum oxide at 50°. Fresh samples of catalyst had to be added from time to time and complete absorption of 3 moles took more than 6 hr. The catalyst was removed, the mixture was evaporated, and the product was recrystallized from ethanol. *Hexahydrobenzflavothebaone trimethyl ether desazamethine* (XVIII) was obtained as colorless prisms, m.p. 253°, $[\alpha]_D^{23}$ +165° ± 2° ($CHCl_3$, *c*, 0.49) λ_{max}: 240; 287 mμ. ϵ_{max}: 74,130; 10,470.

Anal. Calcd. for $C_{30}H_{32}O_5$: C, 76.2; H, 6.8. Found: C, 76.0; H, 6.8.

Dihydrobenzflavothebaone trimethyl ether desazamethine (XVI). The methine (5.7 g.) was heated on the water bath for 90 min. with 30% hydrogen peroxide (17 ml.) and the mixture then evaporated to dryness *in vacuo*. The resulting *N*-oxide was decomposed at 150–170°/15 mm., and the product crystallized from acetic acid. Three grams of *dihydrobenzflavothebaone trimethyl ether desazamethine* (XVI) was obtained as colorless prisms, m.p. 256°, $[\alpha]_D^{19}$ +137° ± 2° ($CHCl_3$, *c*, 0.68).

Anal. Calcd. for $C_{30}H_{28}O_6$: C, 76.8; H, 6.0. Found: C, 76.8; H, 6.1.

Catalytic reduction. Under the conditions described for the catalytic reduction of benzflavothebaone trimethyl ether desazamethine, this compound absorbed 2 moles of hydrogen in 4 hr. giving *hexahydrobenzflavothebaone trimethyl ether desazamethine* (XVIII) as prisms, m.p. 253° alone or mixed with a specimen prepared as in the previous experiment.

Dihydrobenzflavothebaone trimethyl ether desazadihydromethine (XVII). Dihydrobenzflavothebaone trimethyl ether dihydromethine (4.1 g.) was heated on the water bath for 90 min. with 30% hydrogen peroxide (15 ml.). The mixture was evaporated *in vacuo* and the resulting N-oxide decomposed at 150–170°/15 mm. The product was crystallized first from methanol and finally from aqueous acetic acid as colorless prisms, m.p. 257° $[\alpha]_D^{24}$ +215° ± 2° ($CHCl_3$, *c*, 0.48).

Anal. Calcd. for $C_{30}H_{30}O \cdot {}^1/_2H_2O$: C, 75.0; H, 6.5. Found: C, 75.1, 75.0; H, 6.3, 6.3.

Catalytic reduction. Under the conditions already described for the other two desazamethines the desazadihydromethine absorbed 1 mole of hydrogen, giving hexahydrobenzflavothebaone trimethyl ether desazamethine (XVIII), as colorless prisms, m.p. 251°, alone or mixed with material prepared by the hydrogenation of the other two desazamethines. $[\alpha]_D^{23}$ +168° ± 2° ($CHCl_3$, c, 0.49).

Attempts to convert benzflavothebaone trimethyl ether methine into a ψ-methine. Numerous attempts were made to bring about the conversion of benzflavothebaone trimethyl ether methine into a ψ-methine under conditions which were effective in the flavothebaone series (*i.e.* 20% alcoholic potassium hydroxide for 6 hr. under reflux). A crystalline specimen was never obtained and the starting material was never recoverable. The colored tarry products were basic and gave noncrystallizable salts with methyl iodide and with perchloric acid, and attempts at chromatographic purification were also fruitless. The crude ψ-methine gave an intensely blue solution in concentrated sulfuric acid (flavothebaone ψ-methine behaves in a similar way) and its ultraviolet spectrum differed from that of the methine. λ_{max}: 243; 300 (inflection); 340 (inflection) mμ. ϵ_{max}: 89,130; 13,180, 3,980.

Benzflavothebaone trimethyl ether ψ-methine methiodide. Solid potassium hydroxide was slowly added to a solution of benzflavothebaone trimethyl ether methine methiodide (2 g.) in boiling water (80 ml.) and the solution was boiled under reflux for 5 hr. When cold, the droplets of red oil that separated were extracted with chloroform to give a powdery varnish-like solid. Excess of potassium iodide was added to a solution of the crude material in hot water, and, on cooling and shaking, a sticky solid adhered to the flask and it was possible to decant the clear mother liquor, which on further cooling separately deposited colorless needles. The yield of pure benzflavothebaone trimethyl ether ψ-methine methiodide was about 0.1 g. Recrystallization from water brought the m.p. to 253°, depressed to 224° on mixing with the original methine methiodide of m.p. 244°.

λ_{max}: 245; 285 (inflection); 330; 345 mμ. ϵ_{max}: 114,800; 15,140; 8,318; 3,630.

Anal. Calcd. for $C_{32}H_{38}O_5NI$: C, 59.7; H, 6.0; I, 19.7. Found: C, 59.4, 59.4; H, 5.9; I, 19.4.

Bromination of hexahydrobenzflavothebaone trimethyl ether desazamethine. This nitrogen-free product (550 mg.) in chloroform solution (10 ml.) was treated with a standard solution of bromine in chloroform. The addition of 2 molecular equivalents of bromine left only a slight orange color and much hydrogen bromide was evolved; the color of further amounts of bromine was not discharged. The excess of bromine was expelled from the reaction mixture with a current of air and the solvent evaporated to give a viscous brown oil which on trituration with methanol gave a sparingly soluble crystalline solid (490 mg.). Recrystallization from ethyl acetate–methanol and then from acetic acid gave *tribromohexahydrobenzflavothebaone trimethyl ether desazamethine* as colorless needles, m.p. 207° (dec.), $[\alpha]_D^{18}$ +168° ± 6° ($CHCl_3$, *c*, 0.47).

Anal. Calcd. for $C_{30}H_{29}O_5Br_3$: C, 50.6; H, 4.1; Br, 34.2. Found: C, 50.8; H, 4.1; Br, 35.9, 35.4.

Hexahydrobenzflavothebaone trimethyl ether desazamethine oxime was prepared from the ketone (2.0 g.) and hydroxylamine hydrochloride (1 g.) in alcohol-pyridine and was obtained as colorless rods, m.p. 247°, on recrystallization from methanol; $[\alpha]_D^{18}$ +89° ± 3° ($CHCl_3$, *c*, 0.45). Yield 1.78 g.

Anal. Calcd. for $C_{30}H_{33}O_5N$: C, 73.8; H, 6.8; N, 2.9. Found: C, 73.9; H, 6.8; N, 2.8.

Beckmann rearrangement. The oxime (0.80 g.) in chloroform (10 ml.) was cooled in an ice-salt mixture and treated with thionyl chloride (2 ml.). After 1 hr. at room temperature, the volatile materials were evaporated in a stream of air and finally on a steam bath *in vacuo*. The greenish product crystallized from methanol when *hexahydrobenzflavothebaone trimethyl ether desazamethine isoxime* was obtained as slender colorless rods (0.33 g.) m.p. 183. $[\alpha]_D^{18}$ −14° ± 4° ($CHCl_3$, *c*, 0.29).

Anal. Calcd. for $C_{30}H_{33}O_5N$: C, 73.8; H, 6.8; N, 2.9. Found: C, 73.9; H, 6.4; N, 2.9%.

The rearranged oxime was insoluble in water, dilute hydrochloric acid, warm 30% aqueous sodium hydroxide, and hot concentrated hydrochloric acid.

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ABERDEEN, SCOTLAND

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF ARTHRITIS AND METABOLIC DISEASES, NATIONAL INSTITUTES OF HEALTH, DEPARTMENT OF HEALTH, EDUCATION AND WELFARE, PUBLIC HEALTH SERVICE]

Structures Related to Morphine. X.[1] A Position Isomer of (±)-3-Hydroxy-*N*-methylmorphinan (Racemorphan)

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A position isomer (with respect to nitrogen attachment) of (±)-3-hydroxy-*N*-methylmorphinan (Vc), namely 1,2,3,9,-10,10a-hexahydro-6-hydroxy-11-methyl-1,4a(4*H*)-iminoethanophenanthrene (VIIc), has been synthesized. The intermediate ketophenanthrene (VIII) was formed directly from the dinitrile III with refluxing 30% hydrochloric acid. The analgesic potency of VIIc was almost twice that of the deoxy analog (VIIa) but less than 2% of the potency of Vc.

The synthesis of 1,2,3,9,10,10a-hexahydro-11-methyl-1,4a (4*H*)-iminoethanophenanthrene (VIIa) was disclosed in an earlier report.[2] Although VIIa differs structurally from *N*-methylmorphinan (Va)[3] only at the position of closure of the nitrogen ring, it is nevertheless considerably less effective than Va in raising the pain threshold in mice. It has been demonstrated that appropriate substitution of a phenolic hydroxyl (i.e. *meta* to the quaternary carbon) into such moderately active compounds as Va[4,5] and certain benzmorphans[2,6] and phenylmorphans[7] invariably increases analgesic potency and reduces acute toxicity. In order to determine the effect of similar hydroxyl substitution in a compound of a low order of potency, yet one possessing the generally recognized constitutional requirements necessary for the mediation of morphine-like analgesia, the 6-hydroxy derivative (VIIc) of VIIa has been synthesized.

The sequence of reactions used in the synthesis of VIIc was essentially the same as that employed for the deoxy compound (VIIa). The Knoevenagel reaction of 5-(*m*-methoxyphenyl)-2-methyl-9-oxomorphan (I) and malononitrile proceeded normally to give the unsaturated dinitrile (II) in 84% yield. Hydrogenation (platinum oxide) of II was not chemically selective; optimal hydrogen absorption appeared to be 1.1 molecular equivalents and gave a 46% yield of the stereochemically pure, saturated dinitrile (III). However, in contrast to experience in this laboratory with the deoxy series[2] where the dinitrile was hydrolyzed and decarboxylated to the corresponding acetic acid derivative, III was cyclized in 35% yield to the ketophenanthrene (VIII) by refluxing 25–30% hydrochloric acid. The relative ease with which this cyclization[8] takes place may of course be ascribed to the influence of the favorably located, electron-donating, methoxyl group. In addition to VIII a small amount of crystalline phenolic material was isolated. Provisionally it has been assigned the structure IV on the basis of its infrared spectrum (carbonyl absorption at 6.11 μ comparable to that of *p*-hydroxyacetophenone),[9] its ultraviolet spectral pattern, and its elemental analysis. The remainder of the material (intractable) from this experiment was soluble in aqueous sodium hydroxide and gave a rather nondescript infrared diagram showing hydroxyl but little or no carboxyl absorption. Wolff-Kishner reduction of VIII produced VIIb which was converted to the phenol (VIIc) with boiling 48% hydrobromic acid.

Alkali treatment of the methiodide of VIIb and hydrogenation of the methine resulting gave 4a-(2-dimethylaminoethyl)-6-methoxy-1,2,3,4,4a,9,10,-10a-octahydrophenanthrene (VI) identical with the product obtained similarly from (±)-3-methoxy-*N*-methylmorphinan (Vb).[4] As one would predict, more vigorous conditions had to be used to effect the alkaline cleavage of the methiodide of VIIb than were necessary for the methiodide of Vb. On the reasonable assumption that the hydrogen of the tertiary carbon (C_{10a}) is not involved in the Hofmann elimination of VIIb, rings C and B

(1) Paper IX, N. B. Eddy, J. G. Murphy, and E. L. May, *J. Org. Chem.*, 22, 1370 (1957).

(2) E. L. May and J. G. Murphy, *J. Org. Chem.*, 19, 618 (1954). The name heteromorphinan has been suggested for this ring system by Dr. Nathan B. Eddy, Chief, section on analgesics of this institute. Thus VIIc would be 3-hydroxy-*N*-methylheteromorphinan in analogy with the naming of V.

(3) R. Grewe and A. Mondon, *Chem. Ber.*, 81, 279 (1948).

(4) R. Grewe, A. Mondon, and E. Nolte, *Ann.*, 564, 161 (1949).

(5) O. Schnider and A. Grüssner, *Helv. Chim. Acta*, 32, 821 (1949).

(6) E. L. May and E. M. Fry, *J. Org. Chem.*, 22, 1366 (1957).

(7) E. L. May and J. G. Murphy, *J. Org. Chem.*, 20, 1197 (1955).

(8) Presumably III first undergoes cyclization to a hydrogenated phenanthrene β-iminonitrile [*cf.* C. K. Bradsher and D. J. Beavers, *J. Org. Chem.*, 21, 1067 (1956)] which then hydrolyzes and suffers loss of carbon dioxide.

(9) A. H. Soloway and S. L. Friess, *J. Am. Chem. Soc.*, 73, 5000 (1951). There was also a sharp, strong band for IV at 2.89 μ. Infrared analysis of the material resulting from treatment of pure VIII with refluxing 48% hydrobromic acid for a few minutes indicated that it was composed of a mixture of VIII and IV, the former in predominance. If refluxing was continued for 20–30 min., extensive decomposition occurred.

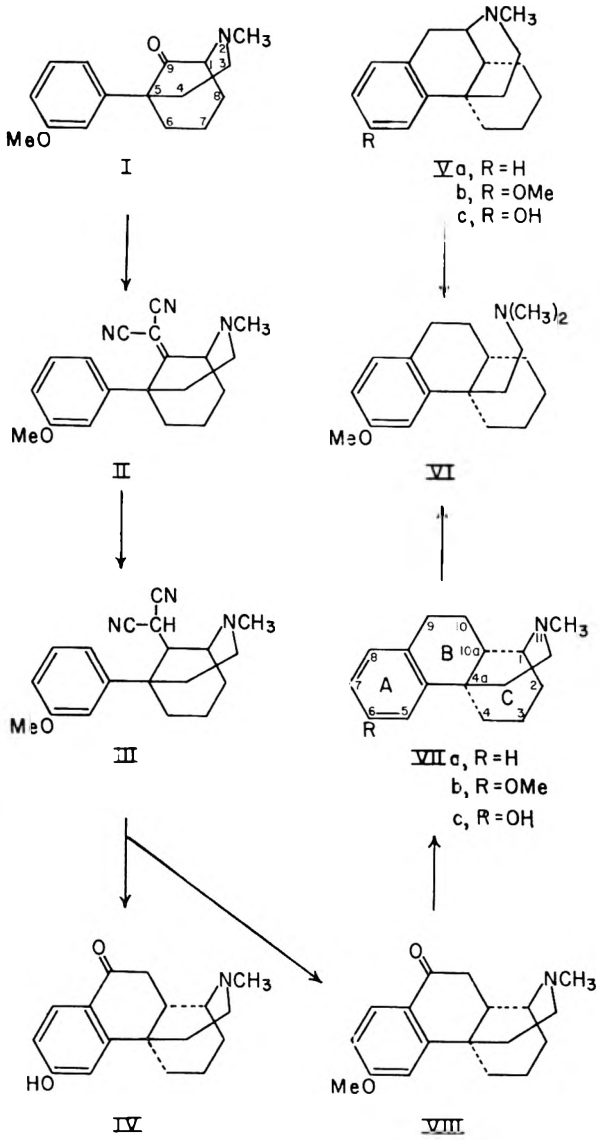


Figure 1

may be designated as cis-fused[2,10] as in the morphinans (V).[4]

The analgesic potency of VIIc was less than twice that of the parent deoxy compound (VIIa) and only 2% of that of the isomeric racemorphan (Vc) as determined in mice. Thus *m*-hydroxylation of VIIa, a compound of relatively low effectiveness, has resulted in a much smaller increase in activity than has been noted earlier for similar substitution in analogous compounds of moderate potency.[1,4,5,7,11]

EXPERIMENTAL

Microanalyses are from the institutes' service analytical laboratory under the direction of Dr. William C. Alford. Melting points were taken in a Hershberg apparatus with total-immersion thermometers. Infrared and ultraviolet spectral data were supplied by Mr. William Jones and Mrs. Ann Wright, respectively, both of this institute.

9-Dicyanomethylene-2-methyl-5-(m-methoxyphenyl)morphan (II) *hydrochloride.* The hydrochloride of I (4.0 g.)[7] was converted to the base (dilute, aqueous ammonia-ether). This base, 1.2 g. of malononitrile, 0.3 g. of ammonium acetate, 0.6 ml. of acetic acid, and 8 ml. of benzene were refluxed vigorously for 1 hr. while collecting the azeotropically distilled water. The solution was diluted to 100 ml. with ether and filtered through Super Cel. Acidification of the filtrate with hydrogen chloride gave a hygroscopic solid which was collected on a sintered glass filter and triturated with 10–12 ml. of warm acetone. Cooling overnight at −5° and filtration gave 3.9 g. (84%) of II hydrochloride, m.p. 200–210°; needles from acetone (after addition of a little ether), m.p. 208–212° (dec.).

Anal. Calcd. for $C_{19}H_{22}ClN_3O$: C, 66.36; H, 6.45. Found: C, 66.47; H, 6.69.

9-(Dicyanomethyl)-2-methyl-5-(m-methoxyphenyl)morphan (III) *hydrochloride.* A mixture of 3.9 g. of II hydrochloride, 0.3 g. of platinum oxide, and 100 ml. of methanol absorbed 1.1 molecular equivalents of hydrogen (at atmospheric pressure) during *ca.* 2 hr., when the absorption rate was fairly constant at 0.75 ml./minute. The reaction was interrupted, and the mixture was treated with a little Norit and filtered through Super Cel. Concentration of the filtrate to 7–8 ml. (water-pump vacuum), seeding, and cooling at −5° for 2–3 hours gave 1.8 g. (46%) of III hydrochloride, m.p. 244–247°. A recrystallization from methanol by addition of a little ether gave analytically pure, oblong plates, m.p. 246–248° (dec.).

Anal. Calcd. for $C_{19}H_{24}ClN_3O$: C, 65.96; H, 6.99. Found: C, 65.53; H, 6.91.

1,2,3,9,10,10a-Hexahydro-6-methoxy-11-methyl-9-oxo-1,4a-(4H)-iminoethanophenanthrene (VIII) *hydrochloride.* The hydrochloride of III (1.8 g.), 17 ml. of concentrated HCl, and 4 ml. of water were refluxed for 16 hr., the solution was evaporated to dryness (water pump), and the residue digested with boiling 1:1 alcohol-acetone. Filtration gave 0.47 g. (84%) of ammonium chloride. The filtrate was evaporated to dryness and the residue partitioned between ether and excess 10% sodium hydroxide. Distillation of the dried ethereal layer gave 0.9 g. of a viscous liquid which, in 5 ml. of acetone was acidified to Congo Red with dry HCl. After 1.5 hr. at −5°, 0.6 g. (35%) of VIII hydrochloride, m.p. 255–260°, was obtained. It was recrystallized to constant melting point with absolute ethanol–ether; long plates, m.p. 261–263°, λ_{max}^{Nujol} 5.96 μ.

Anal.[12] Calcd. for $C_{18}H_{24}ClNO_2$: C, 67.18; H, 7.52; Cl, 11.02. Found: C, 67.54; H, 7.78; Cl, 11.37.

Concentration of the filtrate and washings from the 0.6 g. of VIII hydrochloride gave 0.11 g. of principally needles, m.p. 190–220°. Several recrystallizations from absolute ethanol–acetone gave fine needles, m.p. 191–198°; λ_{max}^{Nujol} 2.89 and 6.11 μ (the latter identical to that reported for *p*-hydroxyacetophenone), λ_{max}^{EtOH} 217, 260, 336 mμ (ϵ 22,000, 13,000, 5,800). On the basis of these data, its solubility in aqueous sodium hydroxide, and the following analytical values the structure (IV) is assigned (*cf.* also footnote 9).

Anal. Calcd. for $C_{17}H_{22}ClNO_2 \cdot {}^1/_2H_2O$: C, 64.42; H, 7.33; N, 4.53. Found: C, 64.05; H, 7.29; N, 4.66.

After drying at 110° the sample gave the following values:

Anal. Calcd. for $C_{17}H_{22}ClNO_2$: C, 66.33; H, 7.21. Found: C, 65.81; H, 7.52.

The 10% sodium hydroxide layer above gave intractable material which showed little or no carboxyl absorption in the infrared

1,2,3,9,10,10a-Hexahydro-6-methoxy-11-methyl-1,4a(4H)-iminoethanophenanthrene (VIIb). The hydrochloride of VIII (0.6 g.), 0.5 g. of potassium hydroxide, 0.5 ml. of 95% hydrazine, and 5 ml. of triethylene glycol were kept at 170–

(10) It follows that addition of hydrogen to II affords III with the H of position 9 *cis* to the $-CH_2CH_2N$ bridge.

(11) O. J. Braenden, N. B. Eddy, and H. Halbach, *Bull. World Health Organization*, **13**, 937 (1955).

(12) After drying to constant weight (loss 2%) at 110° in high vacuum.

180° for 16 hr. and at 200° for 10 min. The cooled solution was treated with water and ether. The dried ether layer was evaporated to give 0.5 g. (98%) of VIIb, m.p. 85–90°; plates from methanol-water, m.p. 93–94°.

Anal. Calcd. for $C_{18}H_{25}NO$: C, 79.66; H, 9.29 Found: C, 79.45; H, 9.02.

The methiodide crystallized from methanol in prisms of m.p. 265–267° (froth).

Anal. Calcd. for $C_{19}H_{28}INO$: C, 55.21; H, 6.83. Found: C, 54.99; H, 6.62.

The hydrochloride crystallized from alcohol-ether in needles which appear to be the hemihydrate.

Anal. Calcd. for $C_{18}H_{26}ClNO \cdot {}^1/_2H_2O$: C, 68.21; H, 8.59. Found: C, 68.02; H, 8.81.

1,2,3,9,10,10a-Hexahydro-6-hydroxy-1-methyl-1,4a(4H)-iminoethanophenanthrene (VIIc). A mixture of 0.4 g. of VIIb and 3 ml. of 48% hydrobromic acid was refluxed for 0.5 hr. and evaporated to dryness *in vacuo*. The residue, digested with 3–5 ml. of absolute alcohol and cooled to 5°, gave 0.4 g. (83%) of VIIc hydrobromide (m.p. 268–272°) which was converted to the base with aqueous ammonium hydroxide; prisms from methanol, m.p. 246–248° (froth).

Anal. Calcd. for $C_{17}H_{23}NO$: C, 79.34; H, 9.01. Found: C, 79.48; H, 9.00.

The *hydrobromide*[13] crystallized from 95% ethanol in small prisms (m.p. 150–155°, froth) which apparently contain one molecular equivalent of solvate ethanol.

Anal. Calcd. for $C_{17}H_{24}NO + C_2H_5OH$: C, 59.37; H, 7.87; Br, 20.80; C_2H_6OH, 11.98. Found: C, 58.75; H, 7.70; Br, 21.45; C_2H_5OH (determined as ethoxyl), 11.73.

4a-(2-Dimethylaminoethyl)-6-methoxy-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (VI) *picrate.* (*a*) *From* Vb. (±)-3-Methoxy-*N*-methylmorphinan (Vb) hydrobromide[5] (0.2 g.) was converted to Vb (aqueous ammonium hydroxide–ether) which in turn gave 0.15 g. of the methiodide (methyl iodide–methanol-ether). This methiodide and 5 ml. of 10% sodium hydroxide were refluxed 1–2 hr. and the resultant base (after drying in ether) was hydrogenated in methanol (5 mg. of platinum oxide) during 10 min. The filtered solution was evaporated to dryness *in vacuo*, and the residue was treated with saturated alcoholic picric acid to give 0.15 g. (79%) of the picrate of m.p. 158–159°. A recrystallization from alcohol did not alter the melting point.

Anal. Calcd. for $C_{25}H_{32}N_4O_8$: C, 58.13; H, 6.25. Found: C, 57.77, 57.91; H, 6.13, 5.95.

(*b*) *From* VIIb. The methiodide of VIIb (0.09 g.), 0.4 g. of potassium hydroxide, 4 ml. of water, and 1 ml. of triethylene glycol were kept at 135–140° (bath temperature)[14] for 3 hr. and treated with water and ether. The residue from the dried ether layer was distilled at 0.5 mm. (bath temperature 150°). The distillate was hydrogenated as described in the previous experiment. The product gave 35 mg. (31%) of picrate, m.p. 145–150°. Careful recrystallization from alcohol yielded 25 mg. of picrate, m.p. 156–157.5°, indistinguishable in crystal form, melting phenomena, and infrared spectrum, from that prepared from Vb.

Acknowledgment. I am indebted to Mr. J. Harrison Ager for valuable assistance in the chemical work and to Dr. Nathan B. Eddy, Chief, section on analgesics, for the pharmacological results.

BETHESDA, MD.

(13) This material was quantitatively convertible to VIIc.

(14) Unlike Vb methiodide, this methiodide (of VIIb) was unaffected by boiling 10% sodium hydroxide.

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

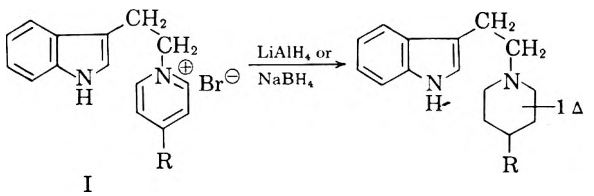
Alstonia Alkaloids. IX. Synthesis of Alstonilinol and Analogs by Reductive Ring Closure[1]

ROBERT C. ELDERFIELD AND BALTHASAR A. FISCHER

Received March 21, 1958

Tetrahydroalstonilinol has been synthesized by reductive ring closure of 2-[β-(6-methoxy-3-indolyl)ethyl]-5-carbomethoxyisoquinolinium bromide. Dehydrogenation of tetrahydroalstonilinol gave alstonilinol.

In a preceding paper the action of lithium aluminum hydride and sodium borohydride upon a series of β-(3-indolylethyl)-1-pyridinium bromides (I) was reported.[2] It was shown that, although two double bonds in the pyridine ring were reduced,



I

no ring closure to a tetracyclic β-carboline resulted. In the present paper we present the results of a study of the action of the two hydrides on β-(3-indolylethyl)-2-isoquinolinium bromides which led to a total synthesis of alstonilinol (XXII). This interesting ring closure to a pentacyclic β-carboline was first described by Robinson and Potts[3] and a preliminary note dealing with our experiences has already appeared.[4]

Inasmuch as the ultimate objective was a synthesis of alstoniline itself which carries a carbomethoxyl group in the 16 position of the parent yohimbane carbon skeleton (disregarding unsatu-

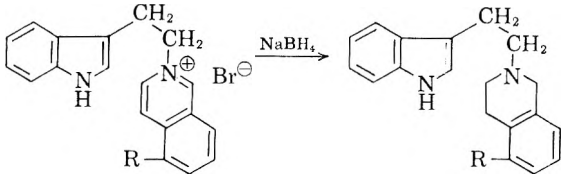
(1) The work here reported was done in part under Research Grant H-1733 from the National Heart Institute and in part under Research Grant CY-2961 from the National Cancer Institute.

(2) R. C. Elderfield, B. Fischer, and J. M. Lagowski, *J. Org. Chem.*, **22**, 1376 (1957).

(3) Sir Robert Robinson and K. T. Potts, *J. Chem. Soc.*, 2675 (1955). *cf.* B. Belleau, *Chem. & Ind.* (*London*), 229 (1955).

(4) R. C. Elderfield and B. Fischer, *J. Org Chem.*, **23**, 332 (1958).

ration in Rings D and E) initial experiments involved a study of the action of sodium borohydride on β-(3-indolylethyl)-2-isoquinolinium bromides carrying a carbomethoxyl function, or some group potentially convertible to such a function, in the 5 position of the isoquinoline system. For this

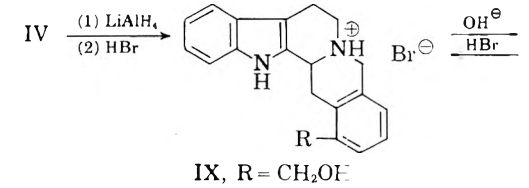


II, R = H
III, R = CN
IV, R = $COOCH_3$

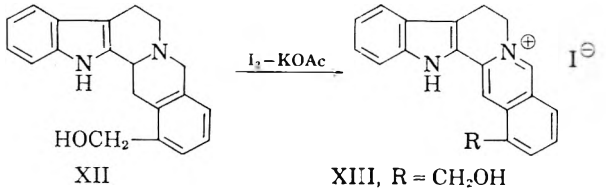
V, R = H
VI, R = CN
VII, R = $COOCH_3$
VIII, R = CH_2OH

purpose the quaternary salts resulting from condensation of β-(3-indolyl)ethyl bromide with isoquinoline (II), 5-cyanoisoquinoline (III),[5] and the methyl ester of isoquinoline-5-carboxylic acid (IV) were selected. Reduction of all three bromides in methanol gave products (V, VI, and VII) which arose by reduction of two double bonds in the pyridine ring of the isoquinoline system without ring closure to a pentacyclic β-carboline. The structure of VII was shown by its identity with the substance obtained by catalytic reduction of IV over platinum and the structures of V and VI are assigned by analogy and on the basis of analytical data. Further, V, VI, and VII all gave a positive Ehrlich color test[6] which is characteristic for indoles in which the α-position is unsubstituted and failed to undergo dehydrogenation with iodine and potassium acetate. The latter reaction is characteristic of reduced pentacyclic β-carbolines.

However, when IV was reduced with sodium borohydride in 95% ethanol reduction of the carbomethoxy group also occurred to give VIII. Although it has been noted previously that reduction of an ester in the analogous pyridinium compounds may take place, the striking effect of merely a change of solvent in the present case is noteworthy. VIII was also obtained by reduction of VII with lithium aluminum hydride.



IX, R = CH_2OH
X, R = CH_2OCOCH_3
XI, R = CHO



XII

XIII, R = CH_2OH
XIV, R = CH_2OCOCH_3
XV, R = CHO

With lithium aluminum hydride III gave an unstable base which has resisted all attempts at purification. On the other hand, IV on reduction with lithium aluminum hydride in a mixture of ether and tetrahydrofuran gave a base (IX) which was isolated as the hydrobromide. IX formed an acetate (X) and the free base (XII) underwent dehydrogenation with iodine and potassium acetate to XIII which in turn gave an acetate (XIV). However, when X was dehydrogenated a compound differing from XIV in melting point was obtained. Only minor differences in the infrared spectra of this substance and XIV were noted. The dehydrogenation product of X also gave analytical data corresponding to those demanded by XIV plus an additional iodine.

Oxidation of IX and XIII with regeneration of the carboxyl group was attempted. With chromic anhydride under various conditions XIII gave an oxygen-free compound. This is under further investigation. With manganese dioxide IX gave a poor yield of the aldehyde (XI) which was very difficult to purify. XI gave a positive test with 2,4-dinitrophenylhydrazine and could be dehydrogenated to XV. The infrared spectra of both XI and XV clearly demonstrated the presence of an aldehyde group.

For the synthesis of alstoniline or derivatives of it by the above general method 6-methoxytryptophol (XVIII) is required. Application of the Japp-Klingemann reaction using *m*-methoxybenzenediazonium chloride and diethyl α-acetoglutarate should give 2-carboxy-6-methoxyindole-3-acetic acid from which XVIII can be prepared by successive decarboxylation and reduction. However, instead of the expected indole derivative, a good yield of a green base which gave analytical data corresponding to $C_9H_{12}N_2O_2$ and which showed an amide band in the infrared was obtained. It formed a yellow salt from which the base could be recovered. The nature of this substance is under further study.

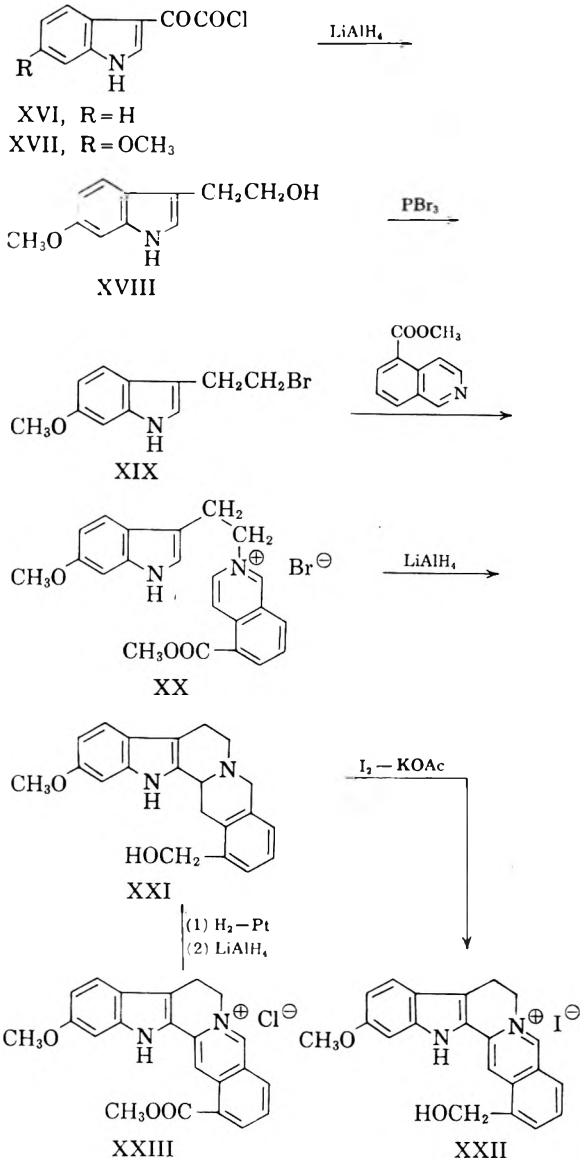
Application of the gramine synthesis as a route to 6-methoxyindole-3-acetic acid using 6-methoxyindole resulted in the formation of a high-melting salt which was not investigated further.

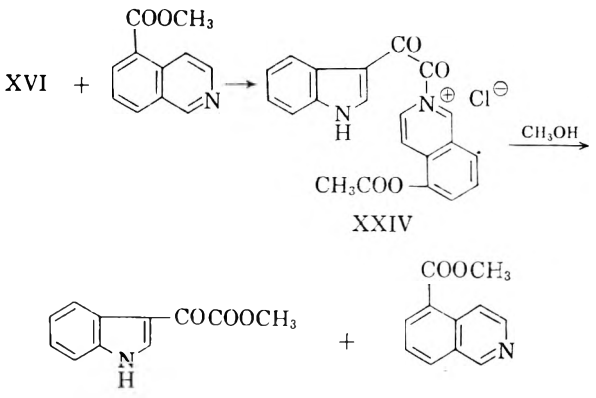
Finally, condensation of 6-methoxyindole with oxalyl chloride[7] to give 6-methoxyindole-3-glyoxalyl chloride (XVII) followed by reduction of XVII with lithium aluminum hydride gave XVIII. Reduction of XVII with sodium borohydride gave the expected

(5) A study of the preferred methods for the preparation of 5-cyanoisoquinoline has been reported by R. C. Elderfield, J. M. Lagowski, O. L. McCurdy, and S. L. Wythe, *J. Org. Chem.*, **23**, 435 (1958).

(6) F. G. Happold and L. Hoyle, *Biochem. J.*, **28**, 1171 (1934). F. Blumenthal, *Biochem. J.*, **19**, 527 (1909).

(7) F. A. Hochstein and A. M. Paradies, *J. Am. Chem. Soc.*, **79**, 5735 (1957).





diol, 6-methoxy-3-(1,2-dihydroxyethyl)indole. The remaining steps to alstonilinol (XXII) are shown in the sequence XVIII–XXII. Alstonilinol as thus prepared was identical in all respects to a sample of the substance prepared from alstoniline (XXIII). The structure previously assigned to alstoniline[8,9] is thus confirmed.

In an effort to accomplish the synthesis in one step, indole-3-glyoxalyl chloride (XVI) was condensed with 5-carbomethoxyisoquinoline. The resulting product (XXIV) underwent methanolysis during recrystallization and this approach was abandoned.

EXPERIMENTAL[10,11]

2-[β-(3-Indolyl)ethyl]-1,2,3,4-tetrahydroisoquinoline (V). To a solution of 3 g. of sodium borohydride in 100 ml. of absolute ethanol one gram of 2-[β-(3-indolyl)ethyl]isoquinolinium bromide[3] was added in small portions. The color of the bromide was discharged immediately. After stirring for 30 min. at room temperature the mixture was refluxed for an additional 30 min. and diluted with 50 ml. of water. After addition of 10 ml. of concentrated hydrochloric acid, the ethanol was removed under reduced pressure. The aqueous solution was made basic with 0.1*N* sodium hydroxide and extracted with ether. After drying over anhydrous sodium sulfate, removal of the ether left 0.61 g. (86%) of material which formed colorless needles, m.p. 124–125°, after recrystallization from acetone. The substance is sensitive to light and moisture. The hydrochloride is an oil, but the picrate, prepared in and recrystallized from aqueous acetone, formed orange needles, m.p. 169° (dec.). Reported m.p. 167–168°.[12] The picrate of the pentacyclic base which would have resulted from ring closure melts at 173° and the free base melts at 188°.[3]

2-[β-(3-Indolyl)ethyl]-5-cyanoisoquinolinium bromide (III). A solution of 2.23 g. of β-(3-indolyl)ethyl bromide, prepared by the action of phosphorus tribromide on tryptophol,[13] and 1.5 g. of 5-cyanoisoquinoline[5] in 50 ml. of methanol was refluxed for 5 min. After standing overnight the yellow solution was concentrated to 20 ml. to give 2.75 g. (73%) of III, m.p. 257° after recrystallization from aqueous ethanol.

Anal. Calcd. for $C_{20}H_{16}BrN_3$: C, 63.49; H, 4.30; N, 11.11. Found: C, 63.51; H, 4.30; N, 11.01.

2-[β-(3-Indolyl)ethyl]-5-carbomethoxyisoquinolinium bromide (IV). A solution of 2.23 g. of β-(3-indolyl)ethyl bromide and 1.87 g. of 5-carbomethoxyisoquinoline[14] in 25 ml. of methanol was refluxed for 5 min. On standing overnight 3.1 g. (75%) of IV, m.p. 248° after recrystallization from a large volume of methanol, separated.

Anal. Calcd. for $C_{21}H_{19}BrN_2O_2$: C, 61.3; H, 4.7; N, 6.8; Br, 19.4. Found: C, 61.2; H, 4.6; N, 6.8; Br, 19.4.

Attempts to condense β-(3-indolyl)ethyl bromide with isoquinoline-5-carboxylic acid failed.

2-[β-(3-Indolyl)ethyl]-5-cyano-1,2,3,4-tetrahydroisoquinoline (VI). Reduction of 1 g. of III with 3 g. of sodium borohydride in 100 ml. of ethanol for 16 hr. at room temperature gave 0.62 g. (77%) of VI as white prisms, m.p. 185–187° after recrystallization from acetone-ether.

Anal. Calcd. for $C_{20}H_{19}N_3$: C, 79.70; H, 6.35; N, 13.94. Found: C, 79.68; H, 6.31; N, 14.02.

The *hydrobromide* of VI, m.p. 222–255° (dec.), was prepared in acetone and recrystallized from methanol.

Anal. Calcd. for $C_{20}H_{20}BrN_3$: C, 62.82; H, 5.27; N, 10.99. Found: C, 62.78; H, 5.30; N, 11.00.

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

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

(10) All melting points are corrected except as noted.

(11) Microanalyses by Spang Microanalytical Laboratory, Ann Arbor, Mich.

(12) E. S. Shaw and D. W. Wooley, *J. Biol. Chem.*, 203, 979 (1953).

(13) B. Jeteles, *Monatsh.*, 15, 807 (1894).

(14) F. T. Tyson, *J. Am. Chem. Soc.*, 61, 183 (1939).

The *picrate* of VI, m.p. 184–187°, was prepared in acetone and recrystallized from ethanol.

Anal. Calcd. for $C_{26}H_{22}N_6O_7$: C, 58.86; H, 4.18; N, 15.84. Found: C, 58.85; H, 4.12; N, 15.75.

Reduction of IV *with sodium borohydride. A. In methanol. 2-[β-(3-Indolyl)ethyl]-5-carbomethoxy-1,2,3,4-tetrahydroisoquinoline* (VII). Reduction of IV in methanol for 4 hr. as in the reduction of VI gave 80% of VII as slightly yellow prisms from acetone, m.p. 130–131°.

Anal. Calcd. for $C_{21}H_{22}N_2O_2$: C, 75.42; H, 6.63; N, 8.38. Found: C, 75.32; H, 6.71; N, 8.39.

The *hydrobromide* of VII formed white needles, m.p. 204–206°, from ethanol.

Anal. Calcd. for $C_{21}H_{23}BrN_2O_2$: C, 60.71; H, 5.58; N, 6.74. Found: C, 60.63; H, 5.70; N, 6.65.

The *picrate* of VII was recrystallized from acetone-ethanol. It melted at 186° or 194° depending on the solvent mixture.

Anal. Calcd. for $C_{27}H_{25}N_5O_9$: C, 57.54; H, 4.47; N, 12.34. Found: C, 57.76; H, 4.16; N, 12.34.

VII was also obtained when the reduction was done in 50% methanol.

B. In 95% ethanol. 2-[β-(3-Indolyl)ethyl]-5-hydroxymethyl-1,2,3,4-tetrahydroisoquinoline (VIII). One gram of IV was added in three portions to a stirred solution of 3 g. of sodium borohydride in 100 ml. of 95% ethanol. The yellow color of the bromide was discharged immediately and the temperature of the mixture rose considerably. After 15 hr. the mixture was worked up as in the preceeding cases giving 0.66 g. (87%) of VIII as fine white needles, m.p. 173–174°, from acetone.

Anal. Calcd. for $C_{20}H_{22}N_2O$: C, 78.40; H, 7.24; N, 9.14. Found: C, 78.17; H, 7.11; N, 9.11.

The *acetate* of VIII was prepared with acetic anhydride in pyridine. It was isolated as the hydrobromide which formed fine white needles, m.p. 214–216°, from methanol.

Anal. Calcd. for $C_{22}H_{25}BrN_2O_2$: C, 61.52; H, 5.86; N, 6.53. Found: C, 61.41; H, 5.84; N, 6.41.

When the reduction was done in absolute ethanol a mixture of VII and VIII was obtained.

VII *By hydrogenation of* IV. Hydrogenation of IV in ethanol over platinum oxide resulted in the uptake of 2 equivalents of hydrogen in 70 min. with the formation of the hydrobromide of VII in 95% yield.

VIII *By reduction of* VII. Reduction of VII with excess lithium aluminum hydride in ether gave VIII, m.p. 173–174°, in 83% yield. The infrared spectra of the free base and its acetate were identical with those of the substances obtained above.

Reduction of IV *with lithium aluminum hydride. 1-Hydroxymethyl-5,7,8,14-tetrahydro-13H-benzo[g]indolo[2,3-a]quinolizine hydrobromide* (IX). To a suspension of 3 g. of IV in a mixture of 300 ml. of anhydrous ether and 300 ml. of anhydrous tetrahydrofuran 3 g. of lithium aluminum hydride was added. After 5 min. white flocks separated. After 30 min. a second portion of 5 g. of lithium aluminum hydride was added and the mixture was stirred for 5 hr. at room temperature and allowed to stand overnight. Excess hydride was decomposed by careful addition of water. After addition of 50 g. of anhydrous sodium sulfate, the salts were filtered off and thoroughly washed with dry ether. The filtrate and washings were concentrated to 15 ml. Addition of hydrobromic acid precipitated the hydrobromide (IX) which formed pale yellow prisms, m.p. 300–301° (dec.), after recrystallization from methanol. The yield was 2.5 g. (67%).

Anal. Calcd. for $C_{20}H_{21}BrN_2O$: C, 62.33; H, 5.49; N, 7.27. Calcd. for $C_{20}H_{23}BrN_2O$: C, 61.99; H, 5.98; N, 7.23. Found: C, 62.24; H, 5.53; N, 7.31.

Attempted hydrogenation of IX over platinum or palladium resulted in no uptake of hydrogen.

1-Hydroxymethyl-5,7,8,14-tetrahydro-13H-benzo[g]indolo-[2,3-a]quinolizine (XII). A suspension of 2 g. of IX in 50 ml. of 50% methanol and 10 ml. of N sodium hydroxide was shaken for 15 min. The slightly brown suspension was filtered, the filter cake was washed thoroughly with water and dried over phosphorus pentoxide. The white powder, 1.5 g. (90%), melted at 230° (dec.). It could not be recrystallized without decomposition. On treatment with alcoholic hydrobromic acid it was reconverted to IX.

The acetate of XII (X) was prepared by allowing 300 mg. of crude XII to stand with a mixture of 10 ml. of acetic anhydride and 10 ml. of pyridine at room temperature for 48 hr. After removal of the solvent at reduced pressure alcoholic hydrobromic acid was added to a solution of the residue in acetone. Recrystallization of the precipitate from methanol gave 295 mg. (75%) of X as colorless prisms which did not melt at 320°. The same compound could also be prepared directly from IX.

Anal. Calcd. for $C_{22}H_{23}BrN_2O_2$: C, 61.82; H, 5.43; N, 6.56. Found: C, 61.84; H, 5.48; N, 6.59.

Dehydrogenation of XII. *1-Hydroxymethyl-7,8-dihydro-13H-benzo[g]indolo[2,3-a]quinolizinium iodide* (XIII). A solution of 40 mg. of XII in 3 ml. of methanol was added to a solution of 200 mg. of potassium acetate and 100 mg. of iodine in 3 ml. of ethanol. After refluxing for 5 min. the brown precipitate was collected and dissolved in methanol. After addition of a few crystals of sodium sulfite, the hot orange solution was filtered. XIII (22 mg.), m.p. 308° (dec.), slowly crystallized as orange needles.

Anal. Calcd. for $C_{20}H_{17}IN_2O$: C, 55.95; H, 4.00; N, 6.53; I, 29.80. Found: C, 56.07; H, 4.11; N, 6.32; I, 29.54.

Acetate of XIII (XIV). A solution of 200 mg. of XIII in 15 ml. of pyridine and 15 ml. of acetic anhydride was shaken for 18 hr. After removal of the solvent under reduced pressure, the residue was suspended in 5 ml. of acetone and the insoluble material was collected. Recrystallization from methanol gave 170 mg. (77%) of fine yellow needles, m.p. above 320° with darkening around 260°.

Anal. Calcd. for $C_{22}H_{19}IN_2O_2$: C, 56.14; H, 4.07; N, 5.95; I, 27.16. Found: C, 56.01; H, 4.00; N, 5.98; I, 26.91.

Dehydrogenation of X. When 40 mg. of X were dehydrogenated as above 27 mg. of brown needles, m.p. 263° (dec.), were obtained. Analysis indicated the presence of two iodine atoms in the compound.

Anal. Calcd. for $C_{22}H_{18}I_2N_2O_2$: C, 44.16; H, 3.03; N, 4.68; I, 41.37. Found: C, 44.91; 44.96; H, 3.27, 3.19; N, 4.61, 4.72; I, 43.01, 42.94.

The infrared spectrum shows a band corresponding to an acetate band, but otherwise the spectrum does not resemble that of XIV.

Oxidation of XIII. Oxidation of the carbinol (XIII) to an aldehyde or acid was attempted with chromic oxide in pyridine, acetone, and aqueous acetone. The product was difficult to purify and decomposed around 325°. The infrared spectrum showed no absorption in the carbonyl or hydroxyl region. Further, analyses confirmed the absence of oxygen in the substance. It is under further investigation.

Anal. Found: C, 66.42; H, 7.29; N, 7.29; I, 20.73.

6-Methoxytryptophol (XVIII). 6-Methoxy-3-indoleglyoxalyl chloride[7,15] (2.06 g.) was added in four portions to a suspension of 4 g. of lithium aluminum hydride in 60 ml. of tetrahydrofuran previously dried over calcium hydride. After standing overnight the excess hydride was destroyed by careful addition of water. The suspension was filtered through Celite and the filter cake was washed thoroughly with ether. After removal of the solvent, the residue was taken up in benzene, dried over sodium sulfate, and recrystallized from benzene to give 1.3 g. (79%) of white plates, m.p. 96–97°.

Anal. Calcd. for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 69.27; H, 6.91; N, 7.16.

β-(6-Methoxy-3-indolyl)ethyl bromide (XIX). To a solution of 1.91 g. of XVIII in 150 ml. of absolute ether 0.9 g. of phosphorus tribromide in 5 ml. of absolute ether was added

(15) 6-Methoxyindole was prepared by a procedure placed at our disposal by Professor R. B. Woodward. We express our appreciation to Professor Woodward for his courtesy.

at 0°. After 15 hr. the supernatant ether solution was decanted, washed once with sodium bicarbonate solution, then with water and dried over anhydrous potassium carbonate. Removal of the ether in a stream of dry air left the bromide which is very sensitive to heat and moisture. It was used directly for the next step.

2-[β-(6-Methoxy-3-indolyl)ethyl]-5-carbomethoxyisoquinolinium bromide (XX). Condensation of XIX with 5-carbomethoxyisoquinoline as in the preparation of IV gave XX as clusters of orange needles, m.p. 270°, with a color change about 220°. The yield was 61% from XIX.

Anal. Calcd. for $C_{22}H_{21}BrN_2O_3$: C, 59.85; H, 4.77; N, 6.35. Found: C, 59.57; H, 4.78; N, 6.35.

Tetrahydroalstonilinol (XXI). To a solution of 441 mg. of XX in 20 ml. of anhydrous tetrahydrofuran and 20 ml. of anhydrous ether was added 1 g. of lithium aluminum hydride. After standing overnight at room temperature with occasional shaking the excess hydride was carefully decomposed with a few drops of water. After filtering through Celite and thorough washing of the filter cake, the solvent was removed under reduced pressure and the residue was recrystallized from chloroform–petroleum ether to yield 210 mg. (64%) of XXI as fine white needles, m.p. 220–224°.

Anal. Calcd. for $C_{21}H_{22}N_2O_2$: C, 75.42; H, 6.63; N, 8.38. Found: C, 75.28; H, 6.77; N, 8.09.

The *hydrochloride* of XXI, prepared in and recrystallized from absolute ethanol, formed white needles, m.p. 278° (dec.) with previous darkening about 250°.

Anal. Calcd. for $C_{21}H_{23}ClN_2O_2$: C, 68.03; H, 6.29; N, 7.51. Found: C, 67.97; H, 6.01; N, 7.29.

The infrared spectra of tetrahydroalstonilinol and its hydrochloride were identical with those of the substances prepared from natural alstoniline (XXIII) according to Elderfield and Wythe.[8]

Alstonilinol (XXII). Dehydrogenation of XXI with iodine and potassium acetate as in the case of XIII gave alstonilinol iodide as orange needles, m.p. 310° (dec.), from methanol. The yield was 90%.

Anal. Calcd. for $C_{21}H_{19}IN_2O_2$: C, 54.90; H, 4.17; N, 6.10; I, 27.86. Found: C, 55.02; H, 4.20; N, 6.07; I, 27.52.

Reaction of β-(3-indole)glyoxalyl chloride (XVI) *with 5-carbomethoxyisoquinoline* (XXIV). To a solution of 2.08 g. of XVI[16] in 15 ml. of tetrahydrofuran was added a solution of 1.87 g. of 5-carbomethoxyisoquinoline in 10 ml. of tetrahydrofuran. When recrystallization of the yellow precipitate from methanol-ether was attempted solvolysis occurred. The crystalline material which separated first as white needles, m.p. 200° (dec.), was identified as the hydrochloride of 5-carbomethoxyisoquinoline by infrared comparison with a known sample.

Anal. Calcd. for $C_{11}H_9NO_2$: C, 59.10; H, 4.48; N, 6.28; Cl, 15.86. Found: C, 59.47; H, 4.49; N, 6.22; Cl, 15.51.

The mother liquors from the above hydrochloride were concentrated and the residue was recrystallized from methanol-benzene to give 1.45 g. (72%) of white prisms, m.p. 226°.

Anal. Calcd. for $C_{11}H_9NO_3$: C, 65.02; H, 4.43; N, 6.85. Found: C, 64.71; H, 4.21; N, 6.64.

Hydrolysis of the above ester with 0.2*N* sodium hydroxide gave an acid, m.p. 214°, after recrystallization from methanol. Indole-3-glyoxylic acid is reported as melting at 216° and its methyl ester at 225°.[17]

Attempted Japp-Klingemann Reaction with m-methoxybenzenediazonium chloride and diethyl α-acetogluturate. To a solution of 24 g. of diethyl α-acetylgluturate[18] in 200 ml. of ethanol and 200 ml. of 20% sodium hydroxide solution at 5° a solution of *m*-methoxybenzenediazonium chloride prepared from 13 g. of *m*-anisidine,[19] 7 g. of sodium nitrite, and 61 ml. of 18% hydrochloric acid was added. The mixture was kept in an ice-salt bath for 3 hr. and allowed to come to room temperature. Green needles, m.p. 130° (14.2 g., 79%), were collected and recrystallized from ethanol.

Anal. Calcd. for $C_9H_{12}N_2O_2$: C, 59.98; H, 6.71; N, 15.55. Found: C, 59.64; H, 6.83; N, 15.66.

The *acid sulfate*, prepared in and recrystallized from 90% ethanol, formed long yellow needles, m.p. 180° (dec.).

Anal. Calcd. for $C_9H_{12}N_2O_2 \cdot H_2SO_4$: C, 38.85; H, 5.07; N, 10.07. Found: C, 38.55; H, 5.10; N, 9.83.

The structure of this green compound is under investigation.

ANN ARBOR, MICH.

(16) M. S. Kharasch, S. S. Kane, and H. C. Brown, *J. Am. Chem. Soc.*, 62, 2243 (1940).

(17) J. N. Baker, *J. Chem. Soc.*, 459 (1940).

(18) The ester, b.p. 134–138° (2 mm.), was prepared in 69% yield by refluxing the product of the condensation of pyrrolidine and ethyl acetoacetate with ethyl acrylate. (Private communication from Dr. R. E. Ireland of these Laboratories.)

(19) P. K. Kadaba and S. P. Massie, *J. Org. Chem.*, 22, 333 (1957).

[CONTRIBUTION FROM THE MERCK SHARP & DOHME RESEARCH LABORATORIES, MERCK & CO., INC.]

Transformations in the D-Homosteroid Series. The Isomeric 17α,17a-Glycols[1]

N. L. WENDLER AND D. TAUB

Received December 30, 1957

The formation and various transformations of the isomeric 17α,17a-dihydroxy-3α-acetoxy-17β-methyl-D-homoetiocholan-11-ones are described.

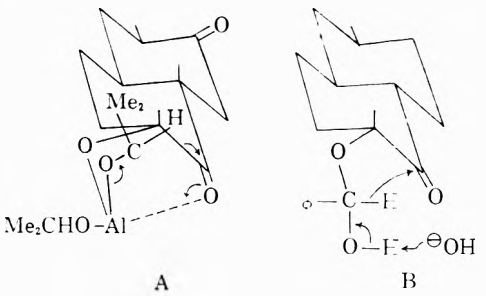
The formation and structure elucidation of two 3α-acetoxy-17α-17a-diols isomeric at position 17a arising from reduction of 3α-acetoxy-17α-hydroxy-17β-methyl-D-homoetiocholane-11,17a-dione (I) were reported recently.[1,2a] Reduction of I with aluminum isopropoxide affords in good yield a glycol, m.p. 213–15° which reverted to I on chromic acid oxidation. When I was refluxed in ethanol solu-

(1) Presented in part at the Symposium on Steroids and Related Natural Products, The Gordon Research Conferences, New Hampton, N. H., July 30–August 3, 1956.

(2) (a) N. L. Wendler, D. Taub, S. Dobriner, and D. K. Fukushima, *Chem. & Ind. (London)*, 1259 (1955); (b) *J. Am. Chem. Soc.*, 78, 5027 (1956).

tion with Raney nickel, there was produced in minor amount (25%) the same glycol, m.p. 213–215° and to a major extent (70%) a new glycol, m.p. 244–246°. The latter on chromic acid oxidation also reverted to I thereby establishing the 17a epimeric character of the two compounds. Saponification of the higher melting (244–246°) isomer produced a triolone, m.p. 250–252° which was identical with material obtained from I by treatment with benzaldehyde and alkali. The formation of the triolone by the latter procedure presumably occurs, as has been pointed out previously,[2a] by way of an unusual crossed Cannizzaro reaction.[3]

Configurational assignment at C-17a was made on the basis of the relative rates of cleavage with periodic acid[4] as well as evidence based on the Wagner rearrangement of their sulfonic ester derivatives (see later). The lower melting glycol reacted within 5 minutes with 1 mole of periodic acid and is assigned the *cis*-configuration (17aα-OH, axial) II; the higher melting glycol, in contrast, required 2 hours for cleavage and is consequently assigned the *trans*-configuration (17aβ-OH, equatorial) III. The transition state for the aluminum isopropoxide reduction of I probably involves coordination of the aluminum with the 17α-hydroxyl and 17a keto groups necessarily from below the ring system as in A.[5] Transfer of hydride ion would



then occur from above (β-face) leading to II. In general aluminum isopropoxide reductions of unhindered ketones lead predominantly to the axial isomers.[6]

The formation of the 17aβ-epimer from the crossed Cannizzaro reaction with benzaldehyde and alkali may be depicted as in B. The C-17 epimer of I[2b] did not react in the Cannizzaro reduction, a result explicable on the basis of steric hindrance to the pertinent transition state on the β-face of ring-D. The crossed Cannizzaro reaction as demonstrated here may prove to have utility as a means for effecting differential reduction of ketolic systems. In the Raney nickel reduction there is a precedent for the predominant formation of the thermodynamically favored 17aβ-equatorial hydroxyl group.[7]

Reaction of either glycol[8] II or III with periodic acid produced a noncrystalline keto aldehyde intermediate (i, footnote 9) which was cyclized under alkaline conditions to the $\Delta^{\alpha\beta}$-unsaturated ketone IV, m.p. 208–210°, $\lambda_{max}^{CH_3OH}$ 237 mμ (12,300).[9] The structure of the $\Delta^{\alpha\beta}$-ketone IV was established by oxidation of its 3 acetate derivative to 3α-acetoxy-11-keto etiobilianic acid[2b] as well as its transformation *inter alia* to the 16 *iso*-analogs of cortisone.[10]

(3) Recently R. B. Turner, M. Perelman, and K. T. Park, Jr., [*J. Am. Chem. Soc.*, 79, 1108 (1957)] have prepared the corresponding 17a epimeric glycol systems in another series.

(4) See for example: P. F. Fleury, J. E. Courtois, and A. Breder, *Bull. soc. chim. France*, 118, (1952).

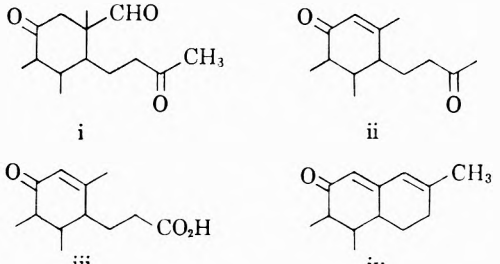
(5) H. Felkin [*Bull. soc. chim. France*, 1050 (1956)] has recently formulated similar transitional intermediates to explain the directional course of reduction of acylic ketols with aluminum alkoxides.

(6) W. Klyne, *Progress in Stereochemistry*, 1, Butterworth Scientific Publications, London, 1954, p. 74.

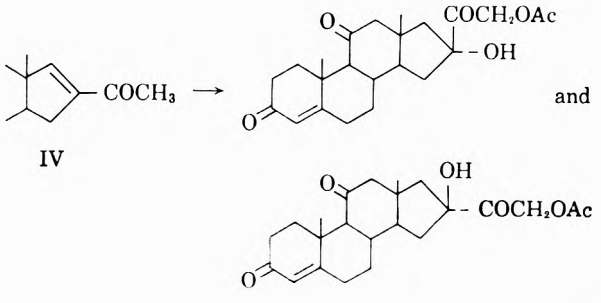
(7) H. Heusser, P. Th. Herzig, A. Fürst, and Pl. A. Plattner, *Helv. Chim. Acta*, 33, 1093 (1950).

(8) For practical purposes, it proved preferable to utilize the triol IIa which was prepared in good yield by one-step reductive D-homoannulation of 3α,17α-dihydroxypregnane 11,20-dione with aluminum isopropoxide–isopropyl alcohol in toluene (see Experimental).

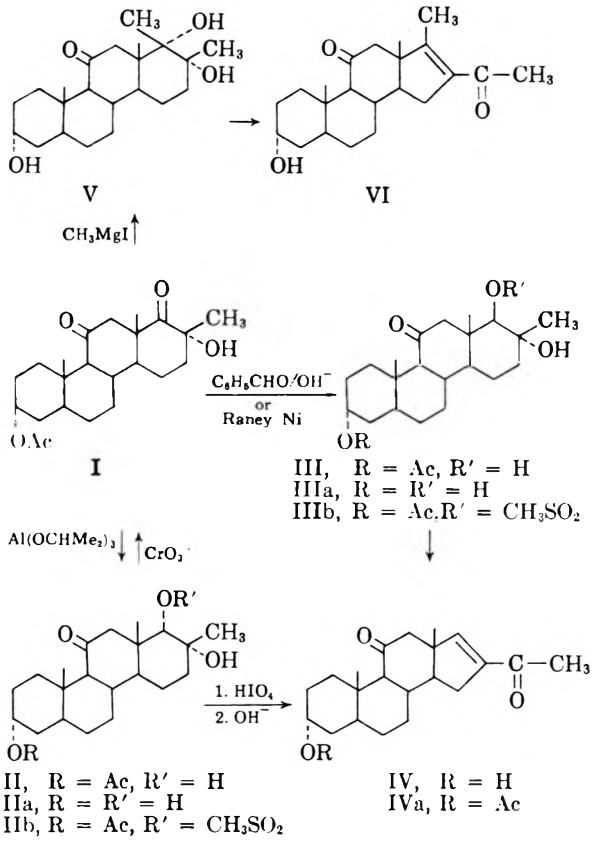
(9) β-Elimination of the formyl group from the intermediate aldehyde i obtained from II and III with periodic acid would give ii which would be expected to have ultraviolet absorption similar to that of IV. However, structure IV can be differentiated from ii on the basis of its empirical formula and the ultraviolet of the semicarbazone derivative λ_{max} 265 mμ (16,800). Semicarbazide would be expected to react with ii at the saturated carbonyl group only to give a semicarbazone with λ_{max} near 230 mμ. In this connection the Δ^{12}-11-keto acid iii [N. L. Wendler, D. Taub, and H. L. Slates, *J. Am. Chem. Soc.*, 77, 3559 (1955)] did not react with carbonyl reagents under the usual conditions. The ultraviolet of the cyclization mother liquors had a shoulder in the 280–290 mμ region possibly indicating the presence of a small amount of iv formed by cyclization of ii.



(10) The transformation series:



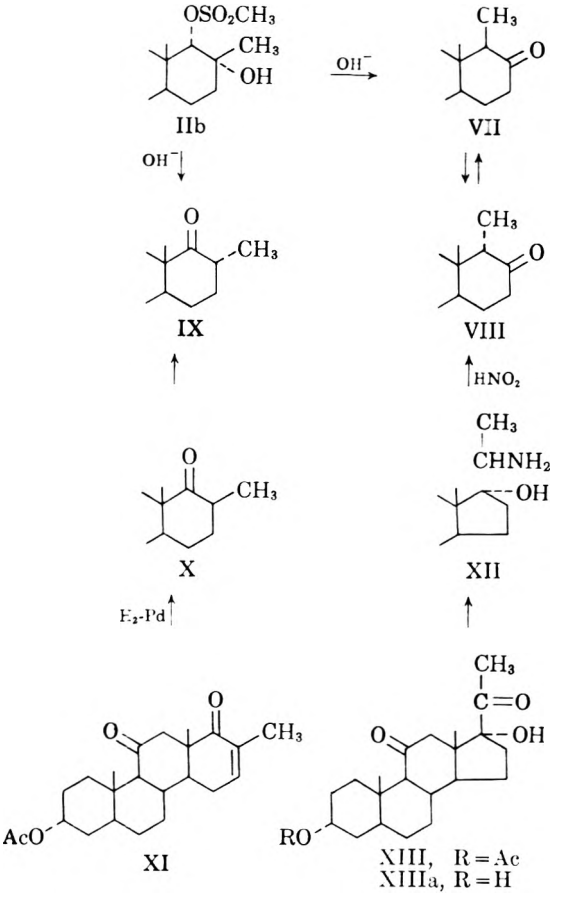
was described on the occasion cited in ref. 1 and will be published in detail at a later date. More recently J. Fajkoš and F. Šorm [*Coll. Czech. Chem. Comm.*, 21, 1013 (1956); *Chem. listy*, 51, 579 (1957)] have prepared systems of the class IV in the 11-desoxy series by another route.



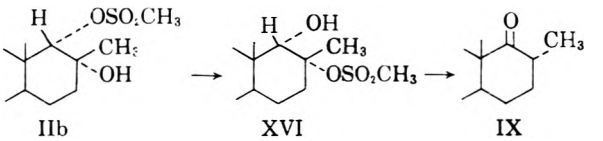
In a like manner reaction of I with methyl Grignard reagent afforded a triol m.p. 197–200° formulated as the *cis* diol V for mechanistic reasons considered to be similarly applicable as in the case of the aluminum isopropoxide reduction (see earlier). Thus a complex formed from the Grignard reagent and I, similar to B, may be envisaged. Cleavage of this glycol with periodic acid followed by alkaline catalyzed ring closure produced the $\Delta^{\alpha\beta}$-ketone VI, m.p. 197–200°, $\lambda_{max}^{CH_3OH}$ 251 mμ (10,300).

Acylation of the *cis*-glycol, II at room temperature or below in pyridine occurs at the 17α-OH. This latter fact was established by acetylation which gave a noncrystalline derivative having OH absorption in the infrared which remained essentially unchanged after chromic acid oxidation. Mesylation of II likewise afforded an amorphous mesylate IIb. Treatment of the latter with methanolic potassium hydroxide caused Wagner rearrangement with production of a mixture of the epimeric 17a methyl ketones VII and VIII as the major product. A sample of the pure 17α-methyl epimer VIII[2b] was prepared by nitrous acid-amine ring-expansion of XII obtained in turn from the oxime of XIII by hydrogenation. Ramirez and Stafiej[11] have shown that this sequence in the 17α-OH series leads to 17aα-methyl 17-ketones. When the 17aα epimer VIII was submitted to alkaline treatment it afforded the same inseparable mixture of VII and VIII as determined by melting point behavior and infrared comparison.[12]

Also formed in small amounts from the alkaline treatment of IIb was the 17α-methyl-17a-ketone IX. The latter proved to be identical with a sample prepared from the $\Delta^{\alpha\beta}$-ketone XI[2b] by hydrogenation followed by alkaline isomerization at C-17. In the latter sequence the hydrogenation of XI is



presumed to proceed from the rear to give the unstable axial 17β-methyl ketone X, m.p. 156–159° which isomerizes with base to the stable equatorial epimer IX, m.p. 165–166° (mixed melting point depressed). The formation of IX from the mesylate derivative IIb is an interesting and perhaps novel change mechanistically. This transformation would appear to be predicated on an initial sulfonyl group transfer 17a-O→17-O with ensuing hydrogen



(11) F. Ramirez and S. Stafiej, *J. Am. Chem. Soc.*, **78**, 644 (1956).

(12) Ramirez and Stafiej (ref. 11) working in another series were quite fortunately able to separate their mixture of 17aα- and 17aβ-methyl epimers by fractional crystallization. They determined the ratio of isomers to be *ca.* 30% 17aα- and 70% 17αβ.

migration C-17a→C-17. The latter phase is by no means an ideal one from the point of view of steric considerations[13] but has, however, some precedent in the formation of hecogenin XV to a minor extent from the alkaline decomposition of XIV.[14] In the latter case a migration of axial hydrogen accompanies the departure of an equatorial mesyloxy function. In analogy it is presumed that the mesylate derivative IIb may rearrange secondarily in a like manner after initial acyl transfer. (IIb → XVI → IX).[15]

The formation of the 17a methyl ketones VII and VIII as the major product from the rearrangement of the mesylate derivative IIb provides additional substantiation for the *cis*-orientation of the functions at 17,17a as ascertained by rate of reaction with periodic acid.

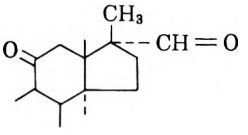
EXPERIMENTAL

3α,17α,17aα-Trihydroxy-17β-methyl-D-homoetiocholane-11-one (IIa). Fifty grams of aluminum isopropoxide was added to a stirred hot solution of 50 g. of pregnane-3α,17α-diol-11,20-dione (XIIIa) in 750 ml. of toluene, 250 ml. of dioxane, and 250 ml. of isopropyl alcohol and the mixture refluxed for 2 hr. At the end of this time the reaction mixture was cooled and 1500 ml. of cold 2*N* HCl was added. The layers were separated and the aqueous phase was extracted three times with ethyl acetate. The combined organic layers were washed with water and saturated salt solution and dried over magnesium sulfate. On concentration *in vacuo* to half the original volume (*ca.* 600 ml.) the triol (IIa) precipitated. The chilled precipitate was filtered, washed with hexane, and dried to give 34.9 g., m.p. 216–220°. Further concentration gave an additional 7 g., m.p. 206–214° (total yield 84%). Recrystallization from acetone-hexane raised the m.p. to 220–225°; λ_{max}^{Nj} 3.00, 5.90 μ.

Anal. Calcd. for $C_{21}H_{34}O_4$: C, 71.96; H, 9.77. Found: C, 72.05; H, 9.51.

Aluminum isopropoxide treatment of 3α-acetoxypregnane-17α-ol-11,20-dione (XIII) in refluxing toluene produced the triol monoacetate II (50%) (see below) as well as considerable (30%) triol (IIa) readily separable on alumina. The formation of the triol (IIa) must be a consequence of ester interchange of the 3α-acetate function with isopropyl alcohol released from the aluminum isopropoxide.

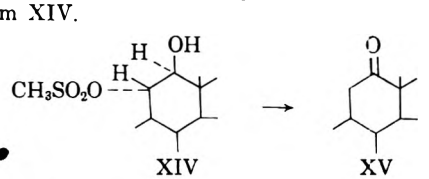
(13) Sterically, ring contraction to



would have been anticipated to follow migration of the sulfonyl group.

(14) N. L. Wendler, R. F. Hirschmann, H. L. Slates, and R. W. Walker, *J. Am. Chem. Soc.*, **77**, 1632 (1955).

(15) Inasmuch as IIb was not obtained crystalline the possibility remains that IX arises from a small amount of a dimesylate species present in IIb. In this event the formation of IX would be comparable to the formation of XV from XIV.



XIV XV

Aluminum isopropoxide reduction of 3α-acetoxy-17α-hydroxy-17β-methyl-D-homoetiocholane-11,17a-dione (I). A solution of 500 mg. of I in 15 cc. of toluene was refluxed for 2 hr. with 500 mg. of aluminum isopropoxide and worked up as described above. Chromatography of the reaction product on alumina afforded 300 mg. of II m.p. 213–215° from acetone-hexane[16] $[\alpha]_D^{Chf}$ +71.9°.

Anal. Calcd. for $C_{23}H_{36}O_6$: C, 70.38; H, 9.24. Found: C, 70.34; H, 9.24.

Raney nickel reduction of 3α-acetoxy-17α-hydroxy-17β-methyl-D-homoetiocholane-11,17a-dione (I). A stirred solution of 3.0 g. of the D-homoketol monoacetate (I) in 150 ml. of absolute ethanol was refluxed 5 hr. with 30 g. of W-4 Raney nickel, which had been partly deactivated by washing with ethyl acetate shortly before use. The reaction mixture was cooled, filtered through celite, and the filtrate taken to dryness *in vacuo*. The crystalline residue (3.0 g.; m.p. 215–230°) was chromatographed on 105 g. of acid-washed alumina. The 20–30% chloroform-benzene eluates afforded 704 mg. (23%) of *3α-acetoxy-17α,17aα-dihydroxy-17β-methyl-D-homoetiocholane-11-one* (II) recrystallized from acetone-ether, m.p. 213–215°; this material was identical with that obtained from the reduction of I with aluminum isopropoxide (see above).

Fractions eluted with chloroform through 5% methanol-chloroform gave 2.0 g. of *3α-acetoxy-17α,17aβ-dihydroxy-17β-methyl-D-homoetiocholane-11-one* (III), which crystallized as needles from acetone-hexane, m.p. 244–246°; $[\alpha]_D^{Chf}$ +75°.

Anal. Calcd. for $C_{23}H_{36}O_5$: C, 70.38; H, 9.24. Found: C, 70.17; H, 9.25.

Saponification of III with sodium hydroxide in aqueous methanol gave the corresponding triol (IIIa) identical with material obtained by Cannizzaro-reduction of I (see below).

Cannizzaro reduction of 3α-acetoxy-17α-hydroxy-17β-methyl-D-homoetiocholane-11,17a dione (I) *with benzaldehyde and alkali.* A solution of 200 mg. of I in 20 cc. of ethanol was treated with 2 cc. of benzaldehyde and 10 cc. of 15% aqueous potassium hydroxide and allowed to stand at room temperature for 18 hr. The product was watered out and crystallized from ethyl acetate to give 100 mg. of IIIa, m.p. 250–252°; $[\alpha]_D^{Me_2CO}$ +55.3°.

Anal. Calcd. for $C_{21}H_{32}O_4$: C, 72.41; H, 9.20. Found: C, 72.14; H, 9.67.

This material was identical with that obtained by saponification of the 244–246° melting monoacetate obtained from the Raney nickel reduction (see above). Conversely acetylation of this triol followed by chromatography yielded some of the 3-monoacetate, m.p. 244–246°.

Chromium trioxide oxidation of 3α-acetoxy-17α,17aβ-dihydroxy-17β-methyl-D-homoetiocholane-11-one (III). To a solution of 198 mg. of the triol monoacetate (III) in 2.0 ml. of acetic acid was added 37 mg. (10% excess) of chromium trioxide in 1 drop of water and 2 ml. of acetic acid. After 17 hr. at 25°, water and chloroform were added and the chloroform extracts were washed with potassium bicarbonate, water, and dried over magnesium sulfate. The crude crystalline neutral product (140 mg.) was purified by chromatography on acid-washed alumina to give prismatic needles with m.p. 155° phase change to hexagonal prisms, m.p. 169–170°, identical with the D-homo ketol (I) by mixed melting point and infrared spectral comparisons.

Chromium trioxide oxidation of 3α-acetoxy-17α,17aα-dihydroxy-17β-methyl-D-homoetiocholane-11-one (II). The isomeric triol monoacetate II, when treated with a slight excess

(16) The D-homoannulation of XIII with "aluminum-*t*-butoxide" in toluene and cyclohexanone, was found to give in addition to I (see ref. 2a) as much as 40% of II. The aluminum *t*-butoxide was commercial reagent obtained from Matheson Co., East Rutherford, N. J. It is believed that this reagent was probably contaminated with an appreciable amount of aluminum isopropoxide which was responsible for reduction of the initially formed I.

over one equivalent of chromium trioxide, as described above, also produced material identical with the D-homoketol I.

Periodic acid cleavage experiments. (A) Cleavage of the cis-glycol 3α-acetate (II). To a solution of the *cis*-glycol 3α-acetate (784 mg.; 2.00 millimoles) in 10 ml. of methanol and 3 ml. of dioxane was added 684 mg. (3.00 millimoles) of periodic acid dihydrate in 10 ml. of water. Iodimetric titration of aliquots[17] showed the reaction to be complete within 5 min. Concentration on the water pump followed by chloroform extraction gave the noncrystalline keto-aldehyde (i).

(B) Cleavage of the cis-glycol 3α-ol (IIa). Similar treatment of the *cis*-glycol 3α-ol (14.00 g.) indicated consumption of an equivalent of periodic acid within 1 min. to give the amorphous keto-aldehyde (i); $\lambda_{max}^{CHCl_3}$ 3.00, 3.70, 5.80, 5.82 μ.

(C) Cleavage of the trans-glycol 3α-acetate (III). Under similar conditions the *trans*-glycol 3α-acetate (589 mg.) required *ca.* 2 hr. to react with an equivalent of periodic acid.

16-Acetyl-Δ[16]-etiocholene-3α-ol-11-one (IV). The keto aldehyde (i) (28 g.) was dissolved in 700 ml. of *t*-butyl alcohol and the air displaced by nitrogen. A solution of 1.30 g. of potassium in 43 ml. of *t*-butyl alcohol was added rapidly to the stirred steroid solution maintained at 20°. After 20 min. the mixture was neutralized with 13.5 ml. of 2.5*N* HCl and the solvent removed *in vacuo*. Saturated salt solution and chloroform were added and the mixture extracted thoroughly with chloroform. The partly crystalline residue was chromatographed on acid-washed alumina (15:1). The eluates from 10% benzene-chloroform to 100% chloroform which contained crystalline material melting over 190° were combined (15.7 g.). Crystallization from acetone-ether gave clusters of needles, m.p. 204–206° with partial softening and phase change to individual needles at 170–180°; $\lambda_{max}^{CH_3OH}$ 237 mμ (12,300); $\lambda_{max}^{CHCl_3}$ 2.79, 2.90–2.95, 5.86, 6.00, 6.24 μ.

Anal. Calcd. for $C_{21}H_{30}O_3$: C, 76.33; H, 9.15. Found: C, 76.21; H, 9.33.

The mother liquors possessed weak absorption in the 280-mμ region indicating the presence of small amounts of a dienone, the quantity of which was increased at the expense of the enone IV by extending the reaction time. This substance was not investigated further.

The periodic acid cleavage product of the *trans*-glycol 3α-acetate (III) when treated with potassium *t*-butoxide as above also gave (IV).

Room temperature acetylation of IV with acetic anhydride in pyridine produced 3α-acetoxy-16-acetyl-Δ[16]-etiocholene-11-one (IVa) which was obtained as a colorless oil; $\lambda_{max}^{CH_3OH}$ 237.5 mμ (10,500); $\lambda_{max}^{CHCl_3}$ 5.82, 5.88, 6.02, 6.27, 8.01 μ.

Oxidation of IVa. The 3-acetate of IV was treated with potassium permanganate as described in reference 2b. The acidic product, m.p. 225–230°, was produced in good yield and was identical with 3α-acetoxy-11-keto-etiobilianic acid by mixed melting point and infrared comparisons.

3α,17α,17aα-Trihydroxy-17β,17aβ-dimethyl-D-homoetiocholane-11-one (V). Methylmagnesium iodide was prepared in ether solution from 2.4 g. of magnesium. After complete reaction the ether was distilled off and replaced with benzene until the distillation temperature reached 65°. To the benzene-ether solution of the Grignard reagent was added dropwise with stirring at room temperature 1.17 g. of I in 20 cc. of benzene. The reaction mixture was refluxed for 1 hr., cooled, and hydrolyzed with water and ammonium chloride. Product crystallized from acetone-hexane, m.p. 208–213°.

Anal. Calcd. for $C_{22}H_{36}O_4$: C, 72.53; H, 9.90. Found: C, 72.66; H, 9.98.

(17) *Scott's Standard Methods of Chemical Analysis*, Fifth Edition; D. Van Nostrand Company, Inc., New York, N. Y., p. 1208.

3α-Hydroxy-17-methyl-16-acetyl-Δ[16]-etiocholene-11-one (VI). A solution of 300 mg. of the triolone (V) in 10 cc. of dioxane was treated with 1 g. of periodic acid in 5 cc. of water for 18 hr. The amorphous product in 10 cc. of methanol was treated with 5 cc. of 15% aqueous potassium hydroxide and refluxed for 2 hr. Concentration of the methanol afforded a product which was crystallized several times from acetone-hexane to give VI m.p. 196.5–200°. $\lambda_{max.}^{CH_3OH}$ 251 mμ (10,320).

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.74; H, 9.30. Found: C, 76.84; H, 9.03.

Acylation of 3α-acetoxy-17α,17aα-dihydroxy-17β-methyl-D-homoetiocholane-11-one (II). Acetylation of II with acetic anhydride in pyridine at room temperature afforded a noncrystalline diacetate exhibiting OH in the infrared. Oxidation of the latter with CrO_3 in acetic acid was essentially without effect as judged by infrared spectral comparison. These observations confirm the structure of a 3α,17aα-diacetate. Similarly mesylation of II (400 mg.) in pyridine (5 cc.) with mesyl chloride (1.5 cc.) at 0–5° for 16 hr. afforded an amorphous mesylate showing OH in its infrared spectrum $\lambda_{max.}^{Nj}$ 2.85–3.02 (OH), 5.8, 8.0 (OAc); 5.85 (C=O), 7.4, 8.5 μ (OSO_2CH_3). This substance is consequently assigned structure IIb.

Alkaline decomposition of 3α-acetoxy-17α-hydroxy-17aα-methanesulfonyloxy-17β-methyl-D-homoetiocholane-11-one (IIb). The product from mesylation of 1 g. of II in 10 cc. of tetrahydrofuran was added to a refluxing solution of 10% sodium methoxide (50 cc.) and refluxed for 2 hr. The reaction mixture was concentrated, the residue extracted and acetylated with acetic anhydride in pyridine. The acetylated product was chromatographed on acid-washed alumina. The eluates consisting of benzene and 1% ether in benzene afforded *3α-acetoxy-17α-methyl-D-homoetiocholane-11,17a-dione* (IX), m.p. 162–163°, not depressed on admixture with an authentic sample prepared from XI → X → IX (see below). The eluates consisting of 5% ether in benzene afforded a mixture of the 17aα and 17aβ-methyl-17 ketones VII and VIII, m.p. 190–210°. This product mixture was identical in the infrared with the product of base isomerization of pure VIII prepared below.

3α-Acetoxy-17β-methyl-D-homoetiocholane-11,17a-dione (X). 3α-Acetoxy-17-methyl-Δ[16]-D-homoetiocholene 11,17a-dione (186 mg.; 0.500 millimole) in 15 ml. of methanol was hydrogenated at atmospheric pressure and 25° over 290 mg. of 25% Pd-on-$CaCO_3$ catalyst. After uptake of one mole of hydrogen (20 min.) the catalyst was removed by filtration and the solvent removed on the water pump. The crystalline residue on two crystallizations from ether–petroleum ether gave 168 mg. of rectangular prisms, m.p. 156–159°, $\lambda_{max.}^{CCl_4}$ 5.76, 5.82, 8.0 μ.

Anal. Calcd for $C_{22}H_{34}O_4$: C, 73.75; H, 9.15. Found: C, 73.60; H, 8.85.

3α-Acetoxy-17α-methyl-D-homoetiocholane-11,17a-dione (IX). To 120 mg. of the 17β-methyl-D-homoetiocholane (X) in 2.0 ml. of methanol was added a solution of 250 mg. of potassium hydroxide in 3.0 ml. of methanol. The mixture was refluxed for 90 min. under nitrogen. The reaction mixture was cooled, water added, and the crystalline 3α-ol filtered and washed with water. Room temperature acetylation in 1 ml. of acetic anhydride and 1 ml. of pyridine for 18 hr. gave the 17α-methyl compound (IX) as needles from ether–petroleum ether, m.p. 164–166°.

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.75; H, 9.15. Found: C, 73.85; H, 8.97.

A mixture melting point of (IX) and (X) depressed to 133–149° and the respective infrared spectra differed in the fingerprint region.

3α-Acetoxy-17aα-methyl-D-homoetiocholane-11,17-dione (VIII). A solution of 3.75 g. of 3α-acetoxy-17α-hydroxy pregnane-11,20-dione (XIII) in 50 cc. of hot methanol was treated with a solution of 3.75 g. of hydroxylamine hydrochloride and 5 g. of sodium acetate in 15–20 cc. of water. Sufficient water was added to maintain homogeneity and

the reaction mixture was refluxed for 1 hr. on a steam bath and allowed to stand at room temperature overnight. The solvents were evaporated and product dissolved in ether and the ether solution washed with water, dried, and concentrated to give the C-20 oxime as a solid, m.p. 216–220°.[18]

Anal. Calcd. for $C_{23}H_{35}O_5N$: C, 68.21; H, 8.69; N, 3.45. Found: C, 68.38; H, 8.91; N, 3.18.

The above oxime (3 g.) was hydrogenated in 30 cc. of acetic acid with 600 mg. of platinum oxide catalyst. The hydrogenation product was filtered, evaporated *in vacuo*, and redissolved in 15 cc. of acetic acid and 45 cc. of water. To the acetic acid solution was slowly added at 0° 5 g. of sodium nitrite dissolved in 5 cc. of water. A gummy oil slowly separated which solidified overnight at room temperature. The solid was extracted with ethyl acetate and the ethyl acetate extract washed free of acid with aqueous potassium bicarbonate solution and dried over magnesium sulfate. The product obtained after evaporation of the solvent was acetylated with pyridine and acetic anhydride and the acetylated product chromatographed on acid-washed alumina. The initial eluate afforded a small amount of the 17a ketone IX. Eluates consisting of 10% to 20% ether in benzene gave an appreciable amount (500 mg.) of a nitrogenous individual (see ref. 9), m.p. 180–183°. Found: C, 65.91, 65.70; H, 8.06 which was not further investigated. The eluates consisting of 5–10% ether in benzene afforded 500–600 mg. of VIII, m.p. 237–240°.

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.75; H, 9.15. Found: C, 73.76; H, 9.02.

Treatment of 150 mg. of VIII in 15 cc. of 10% sodium methoxide in methanol and refluxing for 2 hr. afforded, on working up, a crystalline mixture of VII and VIII from ether, m.p. 193–209°. Mixed melting point with material obtained from alkaline decomposition of IIb 190–212°, the infrared spectra of the two samples were identical.

Acknowledgment. The authors express their appreciation to R. D. Hoffsommer for valuable assistance in the preparation of certain key intermediates.

(18) Prepared by H. Kuo of these Laboratories.

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Microbially Produced 7α- and 7β-Hydroxy-Δ⁴-3-keto Steroids

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Microbial methods for producing 7α- and 7β-hydroxy-Δ⁴-3-keto steroids are described. Progesterone and desoxycorticosterone were converted to their 7α-hydroxylated analogs with a *Helminthosporium* culture and to their 7β-hydroxylated analogs with a *Cladiosporium* culture. Characterization of the 7-hydroxy progesterones was effected by conversion to the common intermediate, Δ⁴,⁶-pregnadiene-3,20-dione. Assignment of configuration is based on the differential rates of oxidation with chromium trioxide.

In examining a wide variety of microbially produced hydroxyprogesterones we have recently encountered two products which upon treatment with methanolic sodium hydroxide showed the shift in ultraviolet absorption maximum from 240 mμ to 285 mμ characteristic of 7-hydroxy-Δ⁴-3-keto steroids.

Characterization of these two isolates as 7-hydroxyprogesterones was accomplished by converting both to Δ⁶-progesterone (Δ⁴,⁶-pregnadiene-3,20-dione) by dehydrating in methanolic sodium hydroxide. Differentiation was established by the different melting points (7α-, m.p. 227–231°, 7β-, m.p. 188–191°) and the nonidentity of the infrared spectra at the longer wave lengths, particularly bands at 9.78 μ and 11.24 μ present in the 7α-hydroxy spectrum and absent in the 7β-hydroxyprogesterone spectrum.

Evidence for the assignment of configuration for the epimeric 7-hydroxyprogesterone was obtained from a study of their relative rates of oxidation with chromium trioxide. Employing the excellent micromethod recently described by Grimmer[1] we found that the epimer produced by the *Helminthosporium* culture (m.p. 227–231°) oxidized much more rapidly than the epimer produced by the *Cladiosporium* culture (m.p. 188–191°). Grimmer reported that under the conditions used axial hydroxyls react more rapidly than the corresponding equatorial epimers. On this basis we have assigned the 7α-hydroxy configuration to the higher melting epimer and conversely the 7β-hydroxy configuration to the lower melting epimer.

No conclusions as to the configuration of the two epimeric 7-hydroxy progesterones could be derived from their optical rotations since both compounds showed nearly identical rotations.

Careful paper strip chromatography, using the system benzene:cyclohexane/formamide:methanol, was successful in differentiating these two compounds. Two points of interest were noted in this chromatogram: (*a*) The 7β (equatorial) epimer was found to be more mobile (17.0 cm. in 30 hr.) than the 7α (axial) epimer (14.0 cm. in 30 hr.). This is the first example, in the hydroxyprogesterone series, of a violation of Savard's rule[2] which proposes that equatorially hydroxylated steroids are more polar than the axial epimers on paper strip chromatograms with Zaffaroni systems.[3]

(1) G. Grimmer, *Angew. Chem.*, 69, 400 (1957).

(2) K. Savard, *J. Biol. Chem.*, 202, 457 (1953).

(3) A. Zaffaroni, R. B. Burton, and E. H. Keutmann, *Science*, 111, 6 (1950).

(*b*) The 7β-hydroxy steroid reduced "blue tetrazolium" whereas the 7α-hydroxy epimer did not. It was this differential tetrazolium reduction by the two epimers which first suggested the assignment of configuration which we arrived at finally. From his comprehensive examination of the behavior of various steroids with the tetrazolium reagent Andre Meyer[4] found that 6α-hydroxyprogesterone (equatorial) was able to reduce tetrazolium salts while the 6β-hydroxy epimer was not. This observation suggested that the 7-hydroxy steroid which reduced tetrazolium chloride was the equatorial epimer 7β-hydroxyprogesterone.

We have assigned the 7α-configuration to the 7-hydroxyprogesterone which we obtained from the incubation of progesterone with *Helminthosporium sp.* The similarities of the physical properties of this product and the 7-OH progesterone reported by Fried *et al.*[5] suggests that the same configuration may be assigned to the Fried product. Also, the 7-hydroxy DOC obtained with *Helminthosporium sp.* corresponds in its physical constants to the 7-hydroxy DOC previously described by Meystre *et al.*,[6] to which they had assigned the 7α-configuration.

EXPERIMENTAL

7α-Hydroxylation. A 3.2-l. fermentation with progesterone (0.8 g.) was carried out with a vegative culture of *Helminthosporium sp.* (Merck collection Number I-39) for 48 hr. The culture filtrate was extracted with ethyl acetate and the extract was fractionated on a Super Cel partition column using the system benzene:formamide. The steroidal substrate was recovered in the initial fractions; further development eluted the 7α-hydroxyprogesterone. The development of the column was followed by paper strip chromatography. The column cuts which were shown to contain only the 7-hydroxy steroid were combined and evaporated to dryness. The residue was crystallized twice from benzene (150 mg.), m.p. 227–231°, $[\alpha]_D^{23°}$ +154 (dioxane, C −0.5), λ_{max}^{MeOH} 242, λ_{max}^{Nujol} 2.85 μ (OH), 5.88 μ (20-carbonyl), 5.99 μ (conjugated carbonyl), 6.15 μ (C=C).

Anal. Calcd. for $C_{21}H_{29}O_3$: C, 76.32; H, 9.15. Found: C, 75.83; H, 9.81.

Conversion of 7α-hydroxyprogesterone to Δ^6 progesterone. The isolate was treated with methanolic sodium hydroxide at reflux temperature for 0.5 hr. Recovery of the product was effected by evaporating the methanol and partitioning the residue between water and Skellysolve C. Concentration of the Skellysolve C to a small volume yielded a crystalline solid which was recrystallized from 100% ethanol, m.p. 140–144°, λ_{max}^{MeOH} 285 mμ. Mixed melting point with an authentic sample of $\Delta^{4,6}$-pregnadiene-3,20-dione gave no depression and the infrared spectra of the reaction product and the authentic sample were identical.

The preparation and isolation of Δ^4-pregnene-7α,21-diol-3,20-dione (7α-OH DOC) was exactly analogous to the method described above for 7α-hydroxyprogesterone. The transformation product, upon recovery from the partition column, was crystallized twice from ethyl acetate, m.p. 216–225°, λ_{max}^{MeOH} 240 mμ, $[\alpha]_D^{25}$ +144° ($CHCl_3$, C = 1). From an 800-mg. fermentation 485 mg. of the 7-hydroxy steroid was recovered. Treatment of this isolate with methanolic sodium hydroxide showed the shift in absorption to 285 mμ characteristic of 7-hydroxysteroids.

7β-Hydroxylation. Employing conditions similar to those described in the previous section a 10-l. fermentation of progesterone (2.8 g.) with the culture *Cladiosporium sp.* (Merck collection Number SF-523) yielded 432 mg. of 7β-hydroxyprogesterone. The isolate was recrystallized from ethyl acetate:petroleum ether, m.p. 188–191°, $[\alpha]_D^{25}$ +141° ($CHCl_3$, C = 1) and $[\alpha]_D^{20}$ +158° (dioxane, C = 0.5) λ_{max}^{MeOH} 242 mμ, E% 472, λ_{max}^{Nujol} 2.9 μ (OH), 5.90 μ (20-carbonyl), 6.01 μ (conjugated carbonyl) and 6.16 μ (C = C).

Anal. Calcd. for $C_{21}H_{29}O_3$: C, 76.32; H, 9.15. Found: C, 76.65; H, 9.02.

This isolate too was converted to $\Delta^{4,6}$-pregnadiene-3,20-dione by refluxing with methanolic sodium hydroxide. Identity was established on the basis of m.p. 140–144°, λ_{max}^{MeOH} 285 mμ, nondepression upon mixed melting with an authentic sample and identical infrared spectra.

7β-Hydroxy-DOC (Δ^4-pregnene-7β,21-diol-3,20-dione) (273 mg.) was isolated from 4 l. of broth from a fermentation of desoxycorticosterone (800 mg.) with *Cladiosporium sp.* The compound was recrystallized twice from ethyl acetate, m.p. 178–181.5°, λ_{max}^{MeOH} 240, $[\alpha]_D^{25}$ +151° ($CHCl_3$, C = 1). Treatment of this isolate with refluxing methanolic sodium hydroxide showed the characteristic shift from λ_{max}^{MeOH} 240 mμ to 285 mμ, indicating dehydration to a dienone.

Chromium trioxide oxidation of 7α- and 7β-hydroxyprogesterone. Approximately 1-micromole (0.46 mg.) samples of the two 7-hydroxyprogesterones were dissolved in equal volumes (3 ml.) of glacial acetic acid in Beckman cuvettes. Three micromoles (0.3 mg.) of chromium trioxide was added to each solution and the optical density at 350 mμ measured immediately. At "zero time" both steroid solutions as well as a blank containing only CrO_3 showed optical density reading slightly in excess of 1.00. Readings were taken every 5 min. and immediately a divergence of rate of oxidation of the two epimers could be detected. Finally after 1 hr. the *Helminthosporium* epimer (m.p. 227–231°) had reduced 50% (o.d. 0.5) of the CrO_3 while the *Cladiosporium* epimer (m.p. 188–191°) had reduced only 25% of the CrO_3 (o.d. 0.75). The blank solution still showed an optical density of 1.00.

RAHWAY, N. J.

(4) Andre S. Meyer and Majoria C. Lindberg, *Anal. Chem.*, **27**, 813 (1955).

(5) J. Fried, R. W. Thoma, D. Perlman, J. E. Herz, and A. Borman, *Recent Progress in Hormone Research XI.* Academic Press, New York, N. Y., 1955.

(6) C. Meystre, E. Vischer, and A. Wettstein, *Helv. Chim. Acta*, **38**, 381 (1955).

[CONTRIBUTION FROM THE CHEMICAL PROCESS IMPROVEMENT DEPARTMENT, LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY]

Absorption Spectra of Some 1-Dehydro Corticosteroids in Concentrated Sulfuric Acid

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A correlation between selective absorption in concentrated sulfuric acid in the 247–267 mμ region and the $\Delta^{1,4}$-3-ketone functional group of several corticosteroids has been made. An associated band in the 295–318 mμ region is also found. The presence of absorption in both the 247–267 mμ and 295–318 mμ region suggests the $\Delta^{1,4}$-3-ketone feature of the corticosteroid molecules.

The use of absorption spectra in concentrated sulfuric acid for characterization and for estimation has become a powerful aid in the study of many classes of steroids. The initial work of Zaffaroni and co-workers[1–3] together with the extensive studies of Bernstein and Lenhard[4,5] provides a comprehensive catalog of selective absorption in concentrated sulfuric acid for several hundred steroids. Selective absorption of steroids in several strong acids has recently been reviewed by Linford.[6]

Certain structural features of the steroid molecule have been related to selective absorption in concentrated sulfuric acid: the α,β-unsaturated carbonyl feature having been correlated with absorption in the 279–300 mμ region,[5] and the isolated carbonyl and hydroxyl group with absorption in the 239–249 mμ region.[5] Some correlations between structure and selective absorption have been made in other strong acid systems.[7–10] The correlation of selective absorption in the 247–267 mμ region and the 295–318 mμ region with the $\Delta^{1,4}$-3-ketone system of the new 1-dehydro corticosteroids is the subject of this report.

None of the simple Δ^4-3-ketones included by Bernstein and Lenhard[4] absorbs in the 247–267 mμ region. Indeed, only three steroids of the 220 listed by Bernstein and Lenhard[4] absorb in the 250–259 mμ region, and these are pregnane and allopregnane derivatives. Only one compound was listed as absorbing in the 260–269 mμ region, 3β-acetoxy-5,7-pregnadien-20-one maleic anhydride adduct (max. 261 mμ). Cevine was also listed as having absorption at 253 mμ and at 263 mμ. Several steroidal sapogenins also have selective absorption in the region 247–267 mμ. under slightly different conditions (94% sulfuric acid). Desoxyhecogenin (268 mμ), hecogenone (269 mμ), sarsasapogenone (267 mμ), smilagenone (268 mμ), and yuccagenin (268 mμ) exhibit bands in this region.[8] In fuming sulfuric acid methoxydoisynolic acid absorbs at 265 mμ.[11] Thus of over 250 steroids described to date only about ten not having the $\Delta^{1,4}$-3-ketone feature absorb in the region of 247–267 mμ. Only one $\Delta^{1,4}$-3-ketone is cited by Bernstein and Lenhard, namely 17β-hydroxy-1,4-androstadiene-3-one (max. 327 mμ), but this steroid does not have selective absorption in the 247–267 mμ region.

An associated band in the region 295–318 mμ is found where the $\Delta^{1,4}$-3-ketone structure is present and selective absorption in the 247–267 mμ region is exhibited. This characteristic absorption, while occurring in most of the cases of $\Delta^{1,4}$-3-ketones cited here (except for No. 8), is not as convincing a correlation as is the case of the 247–267 mμ region correlation, for many steroids absorb in the 295–318 mμ region, and the region overlaps that assigned by Bernstein and Lenhard to the simple α,β-unsaturated ketones.[5] However, Bernstein and Lenhard list only three compounds which absorb in both ranges: veratramine (249 mμ inflection, 311 mμ max., etc.), 3β-acetoxy-5,7-pregnadiene-20-one maleic anhydride adduct (261 mμ inflection, 309 mμ maximum, etc.), and 3β-acetoxy-16α,17α-epoxy-5,7,9(11)-pregnatrien-20-one (259 mμ inflection, 309 mμ inflection). The combination of selective absorption in the 247–267 mμ region and in the 295–318 mμ region is thus suggested as characteristic of the $\Delta^{1,4}$-3-ketone system in the cortical steroid series. Recently maxima for several 1-dehydrocorticosteroids have been reported: 17α,21-dihydroxy-1,4-pregnadiene-

(1) A. Zaffaroni, *J. Am. Chem. Soc.*, **72**, 3828 (1950).
(2) G. Diaz, A. Zaffaroni, G. Rosenkranz, and C. Djerassi, *J. Org. Chem.*, **17**, 747 (1952).
(3) A. Zaffaroni, *Recent Progress in Hormone Research*, **8**, 51 (1953).
(4) S. Bernstein and R. Lenhard, *J. Org. Chem.*, **18**, 1146 (1953).
(5) S. Bernstein and R. Lenhard, *J. Org. Chem.*, **19**, 1269 (1954).
(6) J. H. Linford, *Can. J. Biochem. Physiol.*, **35**, 299 (1957).
(7) J. H. Linford and C. J. Fleming, *Can. J. Med. Sci.*, **31**, 182 (1953).
(8) H. A. Walens, A. Turner, Jr., and M. E. Wall, *Anal. Chem.*, **26**, 325 (1954).
(9) W. J. Nowaczynski and P. R. Steyermark, *Arch. Biochem. Biophys.*, **58**, 453 (1955).
(10) W. J. Nowaczynski and P. R. Steyermark, *Can. J. Biochem. Physiol.*, **34**, 592 (1956).
(11) L. R. Axelrod, *J. Am. Chem. Soc.*, **75**, 6301 (1953).

TABLE I

ABSORPTION SPECTRA IN CONCENTRATED SULFURIC ACID OF SOME STEROIDS

No.	Empirical Formula	Compound	λ_{Max}, Mμ ($E^{1\%}_{1\ cm.}$)[a] 15 Min.	2 Hr.	20 Hr.	λ_{Min}, Mμ ($E^{1\%}_{1\ cm.}$) 15 Min.	2 Hr.	20 Hr.
			C_{21} Steroids					
1	$C_{21}H_{26}O_4$	17α,21-Dihydroxy-1,4,9(11)-pregnatriene-3,20-dione	265(344) 280(256)I 308(190)I 359(259)	267(275)I 278(289) 358(480)	242(482)I 278(377) 285(364)I 354(311) 460(134)	235(292) 325(178)	260(257) 305(177)	262(358) 311(243) 430(128)
2	$C_{21}H_{26}O_5$	17α,21-Dihydroxy-1,4-pregnadiene-3,11,20-trione	264(419) 283(345)I 310(234)I 332–345(141)I 410–428(153)	265(428) 280(393)I 310(243)I 345(179) 410–428(158)	265(430) 280(400)I 347(192) 410(200)I 425(205)	220(142) 372(51)	220(173) 330(170) 371(77)	220(222) 330(176) 370(108)
3	$C_{21}H_{27}O_5F$	9α-Fluoro-11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione	263(364) 308(223)I 375(115) 451(123)	262(341) 308(233)I 372(92)I 451(141)	263(359) 308(259)I 450(167)	228(241) 350(106) 400(89)	237(279) 400(85)	240(311) 385(97)
4	$C_{21}H_{27}O_6Cl$	9α-Chloro-11β,16α,-17α,21-tetrahydroxy-1,4-pregnadiene-3,20-dione	258(244) 262(242)I 315(105) 395(36)	258–262(250) 315(110) 381(65)	258(270)I 264(276) 312(118) 375(82)	220(59) 286(58) 350(13)	220(82) 289(73) 345(29)	220(123) 298(107) 345(49)
5	$C_{21}H_{27}O_6F$	9α-Fluoro-11β,16α,-17α,21-tetrahydroxy-1,4-pregnadiene-3,20-dione	260(334) 310(172) 390(42)	260(346) 310(176) 380(86)	263(386) 310(176) 375(94)	220(63) 287(128) 345(16)	218(71) 288(142) 342(34)	220(80) 300(166) 340(40)
6	$C_{21}H_{28}O_4$	17α,21-Dihydroxy-1,4-pregnadiene-3,20-dione	267(305) 276(286)I 305(239) 345(121)I 426(94)	234(271)I 267(376) 275(370)I 298–307(268)I 343(129)I 385(81)I 420(99) 520(62)	233(317)I 237–274(418) 285(370)I 308(304)I 342(169)I 385(103) 395–415(97)I 500(69)	225(202) 292(235) 373(57)	221(255) 370(66) 465(58)	221(306) 372(88) 460(66)
7	$C_{21}H_{28}O_5$	11β,17α,21-Trihydroxy-1,4-pregnadiene-3,20-dione	240(298)I 262(348) 303(204) 375(239)	240(312)I 265(263) 278(250) 359(353) 390(222)I 470(89)	240(424)I 270–278(300) 355(254) 390(195)I 470(132)	222(250) 289(210) 333(129)	310(183)	321(210)
8	$C_{21}H_{28}O_6$	11β,16α,17α,21-Tetrahydroxy-1,4-pregnadiene-3,20-dione	262(184) 288(124)I 358(256)	235(163)I 244(152)I 280(143) 359(404)	241(308)I 268(272)I 280(260)I 359(285) 500(85)I	227(107) 317(92)	258(133) 308(83)	310(157)
9	$C_{21}H_{29}O_5F$	9α-Fluoro-11β,17α,21-trihydroxy-4-pregnene-3,20-dione	283(478) 319–332(110)I 400(163)I 408(170) 503(68)	283(488) 318–333(138)I 370(139)I 400(167)I 408(174) 503(63)	283(493) 333(147)I 370(147)I 400(181)I 408(184) 502(55) 530(53)	231(158) 353(96) 450(35)	231(162) 352(117) 450(39)	230(173) 353(123) 450(42) 517(50)
10	$C_{21}H_{29}O_6F$	9α-Fluoro-11β,16α,-17α,21-tetrahydroxy-4-pregnene-3,20-dione	284(440) 390(57)	283(462) 380(78)	283(565) 375(78)	227(59) 330(10)	228(65) 325(16)	227(76) 325(25)
11	$C_{21}H_{30}O_5$	17α,21-Dihydroxy-pregnane-3,11,20-trione	340(158) 410–420(158)	232(142)I 250–270(101) 341(206) 410–420(158)	250–270(119) 340(186) 410–420(142) 475(37)I	373(50)	290(83) 370(78)	290(87) 370(87)
			C_{23} Steroids					
12	$C_{23}H_{28}O_4$	21-Acetoxy-4,9(11),16-pregnatriene-3,20-dione	288(438) 387(648)	288(419) 387(708)	288(404) 385(740)	240(155) 326(46)	240(148) 325(42)	239(129) 325(29)
13	$C_{23}H_{28}O_5$	21-Acetoxy-4,16-pregnadiene-3,11,20-trione	285(513) 380(19)	285(550) 380(37)	285(518) 364(125)	335(7)	335(19)	325(46)

TABLE I (*Continued*)

No.	Empirical Formula	Compound	λ_{Max}, Mμ ($E^{1\%}_{1\,cm.}$)[a] 15 Min.	2 Hr.	20 Hr.	λ_{Min}, Mμ ($E^{1\%}_{1\,cm.}$) 15 Min.	2 Hr.	20 Hr.
14	$C_{23}H_{29}O_6F$	21-Acetoxy-9α-fluoro-11β,17α-dihydroxy-1,4-pregnediene-3,20-dione	263(370) 308(228)I 380(141) 410(117)I 452(148)	263(342) 290(275)I 310(247)I 373(114)I 450(171)	264(345) 290(285)I 310(252)I 373(114)I 450(193)	235(268) 350(123) 400(110)	242(291) 390(104)	245(304) 383(107)
		C_{25} Steroids						
15	$C_{25}H_{29}O_8Cl$	16α,21-Diacetoxy-9α-chloro-17α-hydroxy-1,4-pregnadiene-3,11,20-trione	257(285) 311(98)	257(283) 311(98) 390(28)	258(295) 312(107) 390(96)	221(66) 280(59)	221(66) 280(61) 350(12)	220(84) 294(92) 345(30)
16	$C_{25}H_{29}O_8F$	16α,21-Diacetoxy-9α-fluoro-17α-hydroxy-1,4-pregnadiene-3,11,20-trione	258(354) 305(149)	258(354) 305(151) 385(41)	258(354) 307(158) 381(96)	220(74) 279(100)	220(74) 279(100) 345(22)	220(91) 279(144) 342(46)
17	$C_{25}H_{30}O_7$	16α,21-Diacetoxy-17α-hydroxy-1,4,9(11)-pregnatriene-3,20-dione	262(260) 308(115) 355(156)	250(152) 283(101)I 355(423) 520(57)	241(330)I 281(183)I 355(195) 515(196)	230(103) 283(90) 325(102)	238(149) 300(79) 460(52)	310(132) 430(129)
18	$C_{25}H_{30}O_8$	16α,21-Diacetoxy-9β,-11β-epoxy-17α-hydroxy-1,4-pregnadiene-3,20-dione	230(271)I 247–253(208)I 318(163) 415(84) 500(113)I 570(133)	220–230(305) 248–251(259)I 319(200) 405(104) 505(129)I 568(132)	232(339) 252(317)I 316(244) 400(149) 490(149)	290(129) 350(52) 435(81)	285(158) 350(81) 435(91)	221(333) 290(200) 345(105) 435(123)
19	$C_{25}H_{30}O_8$	16α,21-Diacetoxy-17α-hydroxy-1,4-pregnadiene-3,11,20-trione	259(310) 295(142)	259(310) 295(140) 385(27)	259(312) 310(137)I 380(137)	221(63) 281(135)	221(67) 281(138) 345(9)	221(104) 337(43)
20	$C_{25}H_{31}O_8Cl$	16α,21-Diacetoxy-9α-chloro-11β,17α-dihydroxy-1,4-pregnadiene-3,20-dione	258–261(280) 313(109)	258–261(280) 313(112) 382(32)	258–261(299) 313(130) 378(143)	220(66) 285(50)	220(73) 285(57) 345(17)	220(124) 289(100) 342(60)
21	$C_{25}H_{31}O_8F$	16α,21-Diacetoxy-9α-fluoro-11β,17α-dihydroxy-1,4-pregnadiene-3,20-dione	261(297) 308(136)	261(297) 308(136) 380(35)	260(302) 308(133) 375(187) 477(10)I	220(59) 283(88)	220(59) 283(88) 345(17)	217(82) 285(109) 335(50)
22	$C_{25}H_{31}O_8F$	16α,21-Diacetoxy-9α-fluoro-17α-hydroxy-4-pregnene-3,11,20-trione	280(338)	280(338) 390(36)	280(353) 382(90)	230(63)	230(63) 333(14)	230(63) 323(23)
23	$C_{25}H_{32}O_7$	16α,21-Diacetoxy-17α-hydroxy-4,9(11)-pregnadiene-3,20-dione	285(320)	285(313) 380(23)	250(132)I 284(292) 475(146)	233(46)	233(46) 340(16)	230(91) 345(34)
24	$C_{25}H_{32}O_8$	16α,21-Diacetoxy-9β,-11β-epoxy-17α-hydroxy-4-pregnene-3,20-dione	283(317)	282(331) 390(44)	282(350) 380(93) 483(146)	235(111)	239(137) 350(36)	240(173) 340(62) 410(84)
25	$C_{25}H_{32}O_8$	16α,21-Diacetoxy-17α-hydroxy-4-pregnene-3,11,20-trione	283(336)	283(338) 385(30)	281(345) 381(133)	231(57)	231(60) 333(13)	233(77) 322(25)
26	$C_{25}H_{32}O_8$	16α,21-Diacetoxy-11β,-17α-dihydroxy-1,4-pregnadiene-3,20-dione	263(261) 315(125) 338–355(25)	261(148) 353(296)	243(286)I 353(185) 520(164)	221(69) 285(100)	230(109) 300(77)	308(109) 430(108)
27	$C_{25}H_{33}O_8Br$	16α,21-Diacetoxy-9α-bromo-11β,17α-dihydroxy-4-pregnene-3,20-dione	289(277)	289(183)	235(151)I 288(172) 385(64)I	228(68)	239(62)	245(136) 345(47)
28	$C_{25}H_{33}O_8F$	16α,21-Diacetoxy-9α-fluoro-11β,17α-dihydroxy-4-pregnene-3,20-dione	283(373)	283(373) 380(32)	281(379) 377(163)	230(67)	230(67) 324(12)	233(79) 317(19)

[a] I denotes an inflection or plateau.

3,11,20-trione, 263 mμ, 340 mμ (shoulder), 420 mμ;[12] 11β,17α,21-trihydroxy-1,4-pregnadiene-3,20-dione, 267 mμ, 359 mμ;[12] 21-acetoxy-9α-fluoro-11β,17α - dihydroxy - 1,4 - pregnadiene - 3,20 - dione, 262.5 mμ, 310 mμ;[13] 16α,21-diacetoxy-9α-fluoro - 11β,17α - dihydroxy - 1,4 - pregnadiene - 3,20-dione, 261 mμ 308 mμ, 387 mμ.[14]

The time course of selective absorption is of particular value in qualitative identity of several steroids, the characteristic alteration of spectra with time being unique for the several compounds listed. In certain instances the characteristic absorption assigned to the $\Delta^{1,4}$-3-ketone system disappears rapidly, and for this reason measurements must be made at short times by the correlation of spectra and structure of use. The recognition of the $\Delta^{1,4}$-3-ketone system in steroids eluted from paper chromatograms is facilitated with this new correlation.

Comparison of absorption spectra in concentrated sulfuric acid with that in the "100%" phosphoric acid of Nowaczynski and Steyermark[9,10] is made in Table II. Similarities in the 260 mμ region are apparent. A correlation between absorption at 260 mμ in "100%" phosphoric acid and the $\Delta^{1,4}$-3-ketone system was suggested by Nowaczynski and Steyermark.[9,10] From their data there are ten steroids out of some 101 steroids listed that have selective absorption in the 260 mμ region and which do not bear the $\Delta^{1,4}$-3-ketone system; among these are both pregnane and allopregnane derivatives, but there is also one Δ^{4}-3-ketone (6β,17α,21-trihydroxy-4-pregnene-3,20-dione, max 260 mμ). The associated band at 295–318 mμ (concentrated sulfuric acid) is not found for all the $\Delta^{1,4}$-3-ketones in "100%" phosphoric acid. Also this region is correlated with 17-hydroxyl and/or 17-carbonyl groups by Nowaczynski and Steyermark.

TABLE II

COMPARISON OF SELECTIVE ABSORPTION OF $\Delta^{1,4}$-3 KETOSTEROIDS IN CONCENTRATED SULFURIC ACID AND IN "100%" PHOSPHORIC ACID

(I = inflection, plateau)

Compound	Conc. Sulfuric Acid, λ_{max} ($E^{1\%}_{1\ cm.}$)[a]	"100%" Phosphoric Acid, λ_{max} ($E^{1\%}_{1\ cm.}$)
16α,21-Diacetoxy-9α-fluoro-11β,-17α-dihydroxy-1,4-pregnadiene-3,20-dione	260 mμ (302) 308 mμ (133) 375 mμ (187) 475–480 mμ (10) I	260 mμ (299)[b] 290 mμ (213) I 310 mμ (205) I 375 mμ (144)
17α,21-Dihydroxy-1,4-pregnadiene-3,11,20-trione	265 mμ (430) 280 mμ (400) I 347 mμ (192) 410 mμ (200) I 425 mμ (225)	257 mμ (512)[b] 290 mμ (232) I 360 mμ (64) I
11β,17α,21-Trihydroxy-1,4-pregnadiene-3,20-dione	240 mμ (424) I[c] 270–278 mμ (300) 355 mμ (254) 390 mμ (195) I 470 mμ (32)	260 mμ (265)[b] 355 mμ (155) 460 mμ (94) I

[a] Sulfuric acid spectra at 20 hours; 20 hour spectra are thought to be most nearly comparable with the "100%" phosphoric acid spectra as described by Nowaczynski and Steyermark.[9] [b] Calculated from the optical density data for 25 μg./ml. solutions given by Nowaczynski and Steyermark.[10] [c] The data for 20 hours is lacking in absorption in the regions of interest. Both 15 minute and 2 hour data (Table I) show absorption in the 262–265 mμ region.

EXPERIMENTAL

Absorption spectra were determined on a Cary Recording Spectrophotometer Model 11S in essentially the same manner described by Bernstein and Lenhard.[4] Steroid concentration ranged between 25 μg /ml. and 35 μg./ml.; determinations were made at 22°. All steroids used were of high purity as evidenced by combinations of melting point, infrared spectra, ultraviolet spectra, and papergram mobility. The several $\Delta^{1,4}$-3-ketones exhibited absorption in the 6.1–6.25 μ region of the infrared characteristic of the $\Delta^{1,4}$ unsaturated ring A.

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PEARL RIVER, N. Y.

(12) W. R. Slaunwhite and A. A. Sandberg, *J. Clin. Endocrinology & Metabolism*, 17, 395 (1957).

(13) R. F. Hirschmann, R. Miller, R. E. Beyler, L. H. Sarett, and M. Tishler, *J. Am. Chem. Soc.*, 77, 3166 (1955).

(14) S. Bernstein, R. Lenhard, and W. S. Allen, U. S. Patent No. 2,789,118, April 16, 1957.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND PHARMACEUTICAL CHEMISTRY, MEDICAL COLLEGE OF VIRGINIA]

α-Hydroxylamino Nitriles and α-Hydroxylamino Acids[1,2]

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α Hydroxylamino nitriles may be synthesized by (a) treating oximes with dry hydrogen cyanide, (b) allowing appropriate aldehydes or ketones to react with hydroxylamine salt and an alkali cyanide, or (c) allowing oximes to react with an alkali cyanide in the presence of bisulfite. The nitriles may be hydrolyzed to the corresponding α-hydroxylamino acids. The α-hydroxylamino acids may also be obtained from diethylmalonates by first preparing with nitric oxide isonitramino intermediates, which may then be hydrolyzed. The hydroxylamino acids may be reduced in the presence of Pd/C catalyst to their corresponding α-amino acids.

The examination of α-amino acids not normally found in nature for possible antimetabolite activity, particularly for any merit in the chemotherapy of cancer, affords a wide field for study. For example, compounds in which the R group of the general formula R—CH(NH$_2$)—COOH varies over the wide limits open to synthetic means offers one direction for such investigation.[3] Another involves the modifications of the amino group or of the amino-bearing carbon atom. Thus Wilson and Irvin[4] have observed that α-oximino- and α-alkyloximino acids, R—C(=NOH)—COOH and R—C(=NOH′)—COOH, respectively, originally prepared as intermediates for the synthesis of α-amino acids and for use in the synthesis of peptides,[1,5] exhibit inhibition of protein synthesis in Ehrlich ascites carcinoma cells.

A further modification appears in the hydroxylamino analogs of α-amino acids, R—CH(NHOH)—COOH. Nothing is known about their biological properties other than that cycloserine may be looked upon as derived from a hydroxylamine acid.

The hydrogenation of α-oximino acids appeared as an attractive and simple route for their synthesis. Unfortunately, thus far no method or procedure has been found by which this may be accomplished. With sodium amalgam and alcohol, even with an amount calculated to furnish one molecule of hydrogen, α-amino acid and unchanged hydroxylamino acid were isolated. With palladium-charcoal catalyst reducing either the oximino acid or the alkyloximino acid, no change in rate of hydrogenation could be detected to suggest that the hydroxylamino acid is formed as an intermediate; and when the hydrogenation was interrupted after one molecule of hydrogen was taken up, the product was a mixture of α-amino acid and oximino acid.

α-Hydroxylamino nitriles may be prepared by the addition of hydrogen cyanide to oximes, either under anhydrous[6] or appropriate conditions.[7] We have employed the reaction whereby anhydrous hydrogen cyanide, reacting with oximes of simple aliphatic aldehydes forms α-hydroxylamino nitriles. The products obtained in this manner are given in Table I.

$$\text{R—CH(NOH)} + \text{HCN} \rightarrow \text{R—CH(NHOH)—CN}$$

Also it is now found that the Strecker synthesis of α-amino nitriles[8] lends itself to the preparation of α-hydroxylamino nitriles: Thus simple aldehydes

$$\text{R—CHO} + \text{NH}_3\text{OH·Cl} + \text{NaCN} \longrightarrow \text{R—CH(NHOH)—CN} + \text{NaCl}$$

and also ketones such as acetone, cyclopentanone, and others react in the manner indicated. The products prepared by this procedure are indicated in Table I. The reaction is not successful with benzaldehyde, phenylacetaldehyde, hydrocinnamal-

(1) Paper No. 17 in Amino Acid series. For No. 16 see L. M. C. Shen and W. H. Hartung, *J. Org. Chem.*, 23, 96 (1958).

(2) These studies were initiated at the University of North Carolina and continued at the Medical College of Virginia. They were supported by Public Health Service Grant CY-3024, National Institutes of Health, supplemented by funds from the Cancer Institutional Grant, University of North Carolina, by funds from Merck Sharp & Dohme, and assistance from the A. D. Williams Endowment, Medical College of Virginia. For all these the authors express their thanks and appreciation.

(3) J. D. Smith, J. Andrako, and W. E. Weaver, Contract No. SA-43-ph-1807 with the Cancer Chemotherapy National Service Center.

(4) J. E. Wilson and J. L. Irvin, unpublished results.

(5) R. H. Barry and W. H. Hartung, *J. Org. Chem.*, 12, 460 (1947); W. E. Weaver and W. H. Hartung, *J. Org. Chem.*, 15, 741 (1950); W. H. Hartung, D. N. Kramer, and G. P. Hager, *J. Am. Chem. Soc.*, 76, 2251 (1954).

(6) (a) W. v. Miller and J. Plöchl, *Ber.*, 25, 2020 (1892); 26, 1548 (1893). (b) C. C. Porter and L. Hellerman, *J. Am. Chem. Soc.*, 66, 1652 (1944).

(7) (a) H. A. Lillevik, R. L. Hossfeld, H. V. Lindstrom, R. T. Arnold, and R. A. Gortner, *J. Org. Chem.*, 7, 164 (1942). (b) C. C. Porter and L. Hellerman, *J. Am. Chem. Soc.*, 61, 754 (1939). (c) F. Adickes, *J. prakt. Chem.*, 161, 279 (1943).

(8) R. E. Steiger, *Org. Syntheses*, 22, 13 (1942); 24, 9 (1944).

TABLE I

α-HYDROXYLAMINO NITRILES

Compound	Prepared by Procedure	Yield, %	M.P.	Analysis, N Found	Calcd.
$CH_3-CH(NHOH)-CN$[a]	B C	42 50	96–97	31.12	32.56
$CH_3CH_2-CH(NHOH)-CN$[b]	B C	50 65	86–87	27.61	28.00
$(CH_3)_2=C(NHOH)-CN$[c]	B C	60 45	98–99	27.56	28.00
$CH_3CH_2CH_2-CH(NHOH)-CN$[d]	A B C	65 75 90	103–104	24.30	24.58
$(CH_3)_2CH-CH(NHOH)-CN$	A B C	60 80 90	93–94	24.25	24.58
$CH_3CH_2-C(CN)(CH_3)-NHOH$	B C	50 35	60–61	24.18	24.58
$CH_3CH_2CH_2CH_2-CH(NHOH)-CN$	A B C	67 85 95	102–103	20.51	20.88
$(CH_3)_2CHCH_2-CH(NHOH)-CN$[e]	A B C	65 85 95	103–104	20.87	20.88
$CH_2(CH_2)C(CN)(NHOH)CH_2$	B C	95 95	50–52	21.93	22.22
$CH_2(CH_2CH_2)C(CN)(NHOH)CH_2CH_2$[f]	B C	98 95	136–137	19.80	19.99

[a] Reported by v. Miller and Plöchl[6a] m.p. 97°. [b] Reported by v. Miller and Plöchl[6a] m.p. 86–87°. [c] Reported by v. Miller and Plöchl[6a] m.p. 98.5°. [d] Reported by v. Miller and Plöchl[6a] m.p. 102°. [e] Reported by v. Miller and Plöchl[6a] m.p. 103–104°. [f] Calcd. for $C_7H_{12}N_2O$: C, 60.00, H, 8.32, N, 19.99. Found: C, 60.64, 60.66; H, 8.84, 8.67; N, 19.80, 19.60.

dehyde, or acetophenone. With these compounds a change in solvents, longer reaction time, or increase in temperature were of no avail; in each instance only the oxime of the carbonyl compound was isolated. Nor could the desired hydroxylamino nitrile be obtained by allowing the cyanohydrin to react in aqueous medium with hydroxylamine.

Pratt and Richtmyer,[9] treating D-allose with sodium cyanide, obtained a nitrile. In our treatment of aldoximes with sodium cyanide no desired product was formed. However, when the oximes were allowed to react with sodium cyanide in the presence of sodium bisulfite, satisfactory yields of α-hydroxylamino nitriles were obtained, and the product was readily isolated. It is presumed that the reaction proceeds *via* the bisulfite addition product, quite analogous to the conversion of carbonyl bisulfite addition products into their corresponding cyanohydrins.[10] The reaction does not take place

$$R-CH{:}NOH \xrightarrow{NaHSO_3} R-CH(SO_3Na)(NHOH) \xrightarrow{CN^-} R-CH(CN)(NHOH)$$

with the oximes of benzaldehyde or hydrocinnamaldehyde, not even in the presence of phosphate buffer.

The α-hydroxylamino nitriles are colorless crystalline substances, with camphor-like odor, are soluble in alcohol, ether, acetone and other organic solvents except for the petroleum hydrocarbons; they are somewhat soluble in water, the solubility decreasing with increase in molecular weight. They are stable over periods of several weeks to months, slowly decomposing and discoloring on standing. They reduce Fehling's solution and silver nitrate in the cold. They are soluble in dilute acids and may be recovered from acid solution by treatment with base.

When allowed to stand at room temperature in fuming hydrochloric acid for three days the α-hydroxylamino nitriles are hydrolyzed in satisfactory yields to the corresponding α-hydroxylamino acids. The hydrolysis may also be carried out with sulfuric acid, usually in less time, but is more likely to be accompanied by undesirable side reactions.

Another synthesis is an adaptation of the pro-

(9) J. W. Pratt and N. K. Richtmyer, *J. Am. Chem. Soc.*, **77**, 1906 (1955).

(10) L. Neelakantan and W. H. Hartung, data to be published later.

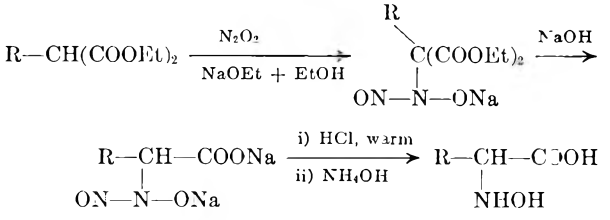
TABLE II

α-HYDROXYLAMINO ACIDS

Compound	Prepared by Procedure	Yield, %	M.P. (dec.)	Analysis N Found	Analysis N Calcd.
$CH_3-CH(NHOH)-COOH$	D	40	194–195	13.00	13.33
$CH_3CH_2-CH(NHOH)-COOH$[a]	D	45	193–194	11.44	11.77
$(CH_3)_2=C(NHOH)-COOH$[b]	D	45	170–171	11.48	11.77
$CH_3CH_2CH_2-CH(NHOH)-COOH$[c]	D E	60 45	194–195	10.34	10.52
$(CH_3)_2CH-CH(NHOH)-COOH$	D	55	192–193	10.32	10.52
$CH_3CH_2-C(CH_3)(NHOH)-COOH$	D	50	140–142	10.28	10.52
$CH_3CH_2CH_2CH_2-CH(NHOH)-COOH$[d]	D E	65 50	194–195	9.90	9.52
$CH_2CH_2-C(CH_2CH_2)(NHOH)-COOH$	D	60	200–202	9.40	9.64
$(CH_3)_2CHCH_2-CH(NHOH)-COOH$	D	60	194–195	9.31	9.92
$C_6H_5CH_2-CH(NHOH)-COOH$[f]	E	65	159–160	7.71	7.73

[a] Reported by v. Miller and Plöchl[6a] m.p. 166–167°. [b] Reported by Munch, *Ber.*, 29, 64 (1896) m.p. 168°. [c] Reported by v. Miller, *Ber.*, 26, 1553 (1893) m.p. 156°. [d] Calcd. for $C_6H_{13}NO_3$: C, 48.96%, H, 8.9%, N, 9.57%. Found: C, 49.11, 49.38; H, 8.37, 8.84; N, 9.95, 10.2. [e] Reported by Traube[11] m.p. 157–158°. [f] Calcd. for $C_9H_{11}NO_3$: C, 49.73, H, 7.64, N, 9.65. Found: C, 50.53, 50.83; H, 7.73, 7.77; N, 9.40, 9.20.

cedure of Traube,[11] who treated an alkylacetoacetic ester with nitrogen oxide, N_2O_2, in the presence of sodium ethoxide to form an isonitramino intermediate which on appropriate hydrolysis afforded the sodium salt of the isonitramino acid. It is found that alkylmalonic esters behave similarly. The products obtained by this reaction are included in Table II.



The α-hydroxylamino acids are stable, colorless crystalline solids, soluble in water, and sparingly soluble in alcohol, ether, acetone, and other usual organic solvents. They melt at quite high temperatures with decomposition. Like their α-amino acid analogs, they are amphoteric, soluble at room temperature in both dilute mineral acids and dilute bases. Their isoelectric points lie between *p*H 6 and *p*H 7. They form stable hydrochlorides. They give a positive ninhydrin reaction. In the presence of formaldehyde, they may be titrated by the Sörensen procedure. In ethanolic solution and in the presence of ammonia they may be reduced with palladium-charcoal catalyst to the corresponding α-amino acids, which may then be further characterized by conversion into some suitable derivative, *e.g.*, the *N*-benzoyl or thiourea derivative.

The α-hydroxylamino acids treated with phenylisothiocyanate, after gentle warming, give a vigorous reaction. However, the only crystalline product thus far isolated from this reaction has been diphenylthiourea, for which the mechanism of formation is not understood. The best yields are obtained when equimolar amounts of reagents are employed. Since hydroxylamine does not give such results, it appears that perhaps this reaction may prove useful in distinguishing between amino acids and hydroxylamino acids.

The infrared absorption spectra of the α-hydroxylamino acids show characteristic bands for the $-COO^-$ and the $-NH_2OH^+$ ions. But thus far attempts to prepare *N*-benzoyl or *N*-acetyl derivatives have been unsuccessful. These possibilities are being explored further.

(11) W. Traube, *Ber.*, 28, 2301 (1895).

EXPERIMENTAL

α-Hydroxylamino nitriles. The data for these compounds are summarized in Table I. Typical syntheses are described.

Procedure A. With 14.0 g. of freshly distilled valeraldoxime (0.139 mole) was mixed 10 ml. of anhydrous hydrogen cyanide (0.2+ mole), and the mixture was allowed to stand for 2 days at room temperature. The solid was sucked dry on a Buchner funnel and washed with petroleum ether; it weighed 12.0 g. (67.7%).

Procedure B. To 21.0 g. of *n*-butyraldehyde (0.3 mole) was added a solution of 23.0 g. of hydroxylamine hydrochloride in 100 ml. water, and then with vigorous stirring was added over a period of 30 min. a solution of 15.2 g. of sodium cyanide (0.31 mole) in 50 ml. water. Stirring was continued for 3 days. The crystalline mass which had formed was sucked dry on a Buchner funnel, washed with a little water, and recrystallized from ether–petroleum ether solvent; 28.5 g. (75%).

Procedure C. Twenty grams of butyraldoxime (0.25 mole) was treated with 12.5 g. of sodium cyanide (0.25 mole) and 72 ml. of a saturated solution of sodium bisulfite; the solution was stirred at room temperature for 3 days. The crystalline mass was filtered off, washed with a little water, and recrystallized from ether–petroleum ether solvent; 25.8 g. (90.4%).

α-Hydroxylamino acids. The data for these are summarized in Table II. Typical experiments for their preparation are given.

Procedure D. A solution prepared from 10 g. of α-hydroxylamino nitrile and 60 ml. of concentrated hydrochloric acid was cooled in an ice bath and saturated with HCl gas, then allowed to stand at 0° for 1 day and at room temperature for 2 more days. The solution was then diluted with 40 ml. of water and refluxed for 6 hr. The water and hydrogen chloride were then removed on a steam bath and at reduced pressure to leave a residue of the α-hydroxylamino acid hydrochloride and ammonium chloride. The desired product was purified by either of two methods.

(1) The residue was taken up in water, decolorized with charcoal, filtered, and the *p*H of the solution was adjusted by the addition of ammonium hydroxide to between 6 and 7; after standing for a day in the refrigerator the solution deposited crystals which were collected on a Buchner funnel, washed with a little cold water, and crystallized from hot water to give colorless product.

(2) The residue was extracted with hot absolute ethanol and filtered; the filtrate was made basic with pyridine and allowed to stand for a day. The crystals were collected and purified as before.

Procedure E. A tenth gram-atom of sodium (2.3 g.) was dissolved in 140 ml. of absolute ethanol, and to the solution was added, with cooling, 5.0 g. of diethyl benzylmalonate (0.1 mole). Nitric oxide (generated by dropping concentrated sulfuric acid on aqueous sodium nitrite) was passed through the solution for 1 hr. and the reaction mixture allowed to stand at room temperature for 1 day. The alcohol was then volatilized at 30° at reduced pressure. To the residue was added 60 ml. of 20% sodium hydroxide solution (approximately 0.3 mole NaOH), allowed to stand at room temperature for a day, and the alkaline solution extracted with ether to remove any unchanged malonic ester. Then, keeping the temperature below 25°, dilute acid was added, and the oil which separated was boiled with 50 ml. concentrated hydrochloric acid for 15 min. The clear solution was cooled and with ammonium hydroxide the *p*H was adjusted to *p*H between 6 and 7. The crystalline colorless precipitate was collected on a Buchner funnel, washed with a little cold water, and then recrystallized from hot water; 10.0 g. (55.4%).

Reduction of α-hydroxylamino acids. Five grams of α-hydroxylaminovaleric acid in 30 ml. concentrated ammonium hydroxide solution, diluted by addition of 10 ml. water, was shaken on a Parr apparatus in hydrogen at four atmospheres pressure with 1 g. of palladium-charcoal catalyst. After 8 hr. the catalyst was filtered off, and the solution was evaporated to dryness; the residue weighed 3.5 g. The *N*-formyl derivative melted at 132–133°; reported 132°.[12]

In a similar manner β-phenyl-α-hydroxylaminopropionic acid was converted to β-phenylalanine, which was identified as its *N*-benzoyl derivative, m.p. 188–189°; reported 187–188°.[13] α-Hydroxylaminocaproic acid was reduced to α-aminocaproic acid, of which the *N*-formyl derivative melted at 115°; reported 113–115°.[14]

1-Hydroxylamino-1-cyclopentanecarboxylic acid was reduced to 1-amino-1-cyclopentanecarboxylic acid, hydrochloride salt, m.p. 222–224° (dec.) agreeing with the value observed for an authentic sample of the hydrochloride.[15] After hydrogenation, the product no longer reduced Fehling's solution or silver nitrate solution.

RICHMOND, VA.

(12) E. Abderhalden, *Chem. Zentr.*, **1921**, III, 296.
(13) E. Fischer and A. Mouneyrat, *Ber.*, **33**, 2383 (1900).
(14) D. Marko, *Ann.*, **362**, 333 (1908).
(15) L. Neelakantan, unpublished result.

[CONTRIBUTION FROM THE UNIVERSITY OF NORTH CAROLINA]

Methyl Ketone Isosters of α-Amino Acids[1]

KENNETH L. HOY[2] AND WALTER H. HARTUNG[3]

Received February 7, 1958

In the many correlations between the structure of organic compounds and their physiological activity the sequence of the four atoms $=N-\underset{|}{\overset{|}{C}}-\underset{|}{\overset{|}{C}}-O-$ seems to be of considerable significance, for it appears in many substances exhibiting varied pharmacodynamic properties. Thus, compounds in which the oxygen atom appears as an alcoholic hydroxyl or its derivatives include acetylcholine, procaine, methantheline, epinephrine, chloroamphenicol, diphenhydramine, and the cinchona alkaloids, to name only a few. In the α-amino acids is found the same sequence, but with the terminal carbon as a carboxyl group; these are so numerous and of such importance as to constitute a specialized area in both organic and biological chemistry.

(1) Paper number 18 in the amino acid series. For number 17 see L. Neelakantan and W. H. Hartung, *J. Org. Chem.*, **23**, 964 (1958).
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(3) Present address: Medical College of Virginia, Richmond, Va.

Knowing the bond angles and employing Pauling's bond radii[4] one may calculate the distances between the oxygen and nitrogen atoms in this four-atom sequence for both the *cisoid* and *transoid* conformations. These values are given in Table I.

The biological activity of the amino alcohols and of the amino acids in which the $=N-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-O-$ sequence occurs suggests that in these compounds the distance between the N and the O atoms is optimum, permitting the compounds to lodge on the receptor site of the tissue. The particular site on which they lodge, that is, the characteristic reaction provoked in the tissues is then determined by the nature and the magnitude of the substituents present in the $=N-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-O-$ grouping.

In the hypothetical oxidation of the amino alcohols to the amino acids the amino aldehydes, $=N-\overset{|}{\underset{|}{C}}-\overset{H}{\underset{|}{C}}=O$, and the amino ketones, $=N-\overset{|}{\underset{|}{C}}-\overset{R}{\underset{|}{C}}=O$, appear as intermediate stages and, according to the calculations given in Table I, they may also be expected to exhibit a high degree of physiological activity, since the distances between the N and O atoms, in both conformations, is similar to that for amino alcohols and amino acids. Again, the exact nature of the physiological response will be conditioned, it may be expected, by the substituents present in this four-atom grouping.

With these thoughts in mind, an exploratory investigation was undertaken for procedures which may be adapted for the synthesis of methyl ketones of general structure $R-\underset{|}{\underset{NH_3Cl}{CH}}-CO-CH_3$, which may be regarded as structural isosters of the α-amino acids. The experimental work is summarized schematically as follows:[5]

(4) L. Pauling, *The Nature of the Chemical Bond*, Cornell University Press, 2nd ed., Ithaca, 1945, Chapter V.

(5) Many such ketones are described in the chemical literature, and they were prepared by various procedures. It is not the purpose of this report to review the various methods of synthesis and comment on them. Some will be found in the references cited.

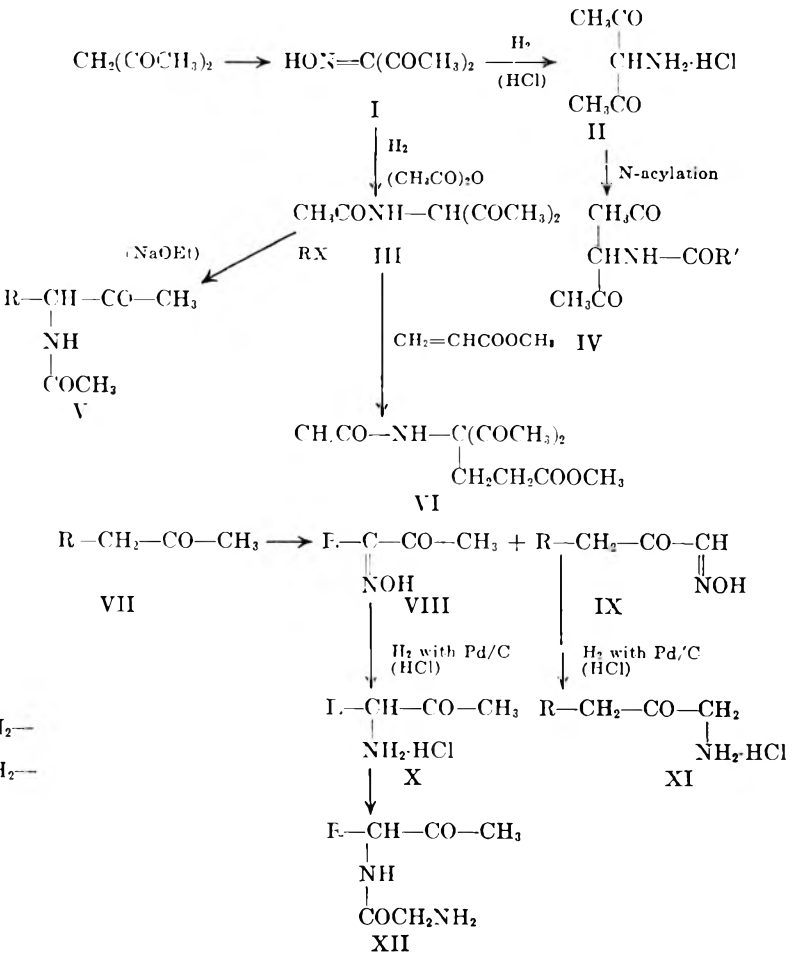


TABLE I

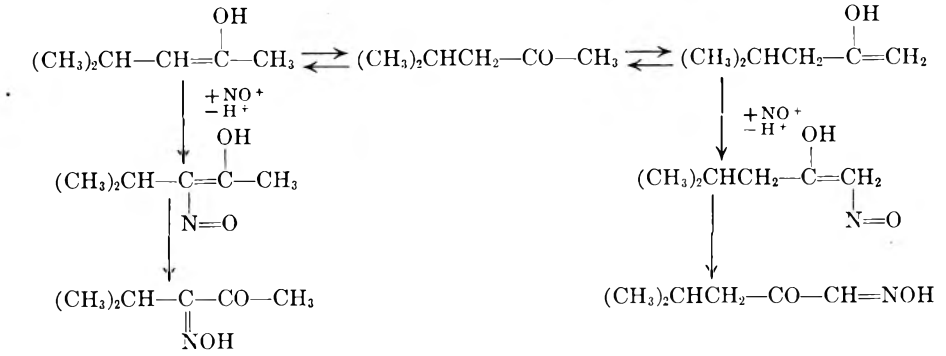
CALCULATED N TO O DISTANCES FOR VARIOUS MODIFICATIONS OF THE N—C—C—O SEQUENCES

Modification	Conformation	Distance between	A
=N—C—C—O	*Cisoid*	N and —O—	2.51
	Transoid		3.73
=N—C—C=O	*Cisoid*	N and =O	2.76
	Transoid		3.62
=N—C—C=O (O)	*Cisoid*	N and =O	2.76
	Transoid		3.62
	Cisoid	N and —O—	2.51
	Transoid		3.73

The instability of the dipeptide analogs XIIa and XIIc, even in the form of their hydrochloride salts, was unexpected. This is undoubtedly a function of the amino group of the glycine moiety, along with the carbonyl group, for the intermediate carbobenzyloxy derivatives, from which they were prepared by hydrogenolysis, are quite stable. This suggests that a tripeptide analog will be more stable. The conversion of II to IV anticipates the formation of peptide-like compounds in which one terminal component is aminoacetone.

The formation of two isomeric oximino ketones during the nitrosation of 4-methyl-2-pentanone, VIIa, is probably typical for this reaction with all compounds of type VII. It was not established early enough to encourage the isolation of the isomers of type IX, except for IXa.

The results suggest that the nitrosation reaction is quite comparable to the bromination of such ketones in acidic media; and the proportion of the oximino isomers formed corresponds favorably with the analogous bromo isomers. It has been shown that bromination involves substitution on the enol form of the ketone.[6] For the formation of the oximino ketones the reaction then becomes as follows:



The nitrosoenolate, where possible will rearrange to the isomeric oximino ketone.[7]

(6) (a) P. D. Bartlett and C. H. Stauffer, *J. Am. Chem. Soc.*, **57**, 2580 (1935). (b) G. W. Wheland, *Advanced Organic Chemistry*, 2nd. ed. John Wiley and Sons, New York, 1951, p. 256.

(7) O. Touster, *Org. Reactions*, **VII**, 327–380 (1953).

EXPERIMENTAL

3-Oximino-2,4-pentanedione, I, was prepared by the procedure of Wolff and coworkers[8] in yields of 92% of theory. Crystallized from ligroin-benzene 1:6, it formed white crystals, m.p. 75–76°; reported m.p. 75°.[8]

Nitrosation of 4-methyl-2-pentanone, VIIa[9]. In a 500-ml. three-neck flask fitted with a sealed stirrer, dropping funnel, and a reflux condenser, was placed a solution of 50 g. (0.5 mole) of 4-methyl-2-pentanone in 300 ml. of dry ether and 50 ml. of anhydrous ethanol containing 0.00735 mole HCl/ml. Cooled to −5° there was added to the stirred solution 44.5 g. (0.5 mole) of freshly distilled isopropyl nitrite at such a rate that the color did not become darker than light orange and the temperature did not rise above 5°; stirring and cooling was continued for another 30 min., after which the reaction mixture was transferred to a one-liter separatory funnel and extracted with three 100-ml. portions of 10% sodium hydroxide solution. The combined alkaline extracts were cooled to 0° and slowly acidified with concentrated HCl to *p*H 3. On standing, an oily solid formed; this was collected on a Buchner funnel and pressed as dry as possible.

The solid was crystallized from ligroin; it weighed 32.0 g. (49.5%) and melted at 76–77° (reported m.p. 75°[10] and 76°[11]). A sample of the crystals treated with 2,4-dinitrophenylhydrazine formed orange colored prisms, which, crystallized from acetone and water, melted at 202°.

Anal. Calcd. for $C_{12}H_{18}N_5O_5$: C, 46.60; H, 4.89; N, 22.65. Found:[12] C, 46.22, 46.30; H, 4.75, 4.78; N, 22.4, 22.4.

The ligroin mother liquors from which the 4-methyl-3-oximino-2-pentanone had been crystallized contained a small amount of insoluble brown oil; this with the oil pressed from the crystals weighed 15.0 g. A sample of this crude oil treated with 2,4-dinitrophenylhydrazine formed red needles which, crystallized from acetone and water, melted at 234–235°. This was the dinitrophenylhydrazone of 4-methyl-1-oximino-2-pentanone (of IXa).

Anal. Calcd. for $C_{12}H_{18}N_5O_5$, C, 46.60%; H, 4.89%; N, 22.65%. Found:[12] C, 46.76, 46.56%; H, 4.33, 4.48%; N, 21.3, 21.2%.

Catalytic reduction of the crude oil in ethanolic HCl and the isolation of the hydrochloride of 4-methyl-1-amino-2-pentanone, m.p. 178–180°, described as m.p. 179–180°,[13] establishes this crude oil as consisting predominantly of 4-methyl-1-oximino-2-pentanone, IXa.

The nitrosation was repeated with 10.00 g. (0.100 mole) of 4-methyl-2-pentanone. After the reaction was complete, the solvent was volatilized. One hundredth of the residue, representing 0.001 mole, was treated with 2,4-dinitrophenylhy-

(8) V. Wolff, P. Block, G. Lorentz, and P. Trappe, *Ann.*, **325**, 134 (1902).

(9) This ketone was prepared by the reduction of mesityl oxide.

(10) B. Westenberger, *Ber.*, **16**, 2991 (1883).

(11) F. Lehmann, A. Bretscher, H. Kuhn, E. Sorkin, M. Erne, and H. Erlenmeyer, *Helv. Chim. Acta*, **33**, 1224 (1950).

drazine, depositing red-orange crystals; these, when dried, weighed 158.3 mg. and were taken up in 100.0 ml. of dioxane. Of this solution 10 ml. was passed through a column of alumina 2 cm. × 16 cm. previously washed with dioxane. The chromatogram, developed with dioxane, appeared as three distinct bands; each was separately eluted with 50% ether-dioxane. The product from the lowest band was identified as the 2,4-dinitrophenylhydrazone of 4-methyl-1-oximino-2-pentanone, m.p. 233–234°. The middle band comprised the dinitrophenylhydrazone of 4-methyl-3-oximino-2-pentanone, m.p. 200–203°. The top band was the 2,4-dinitrophenylhydrazone of unreacted 4-methyl-2-pentanone, m.p. 92–94°. The top product was not completely removed. As determined from a known mixture of the three dinitrophenylhydrazones, it was calculated that elution of the dinitrophenylhydrazones of the two oximino ketones afforded 94 to 96% recovery.

The separate eluates were isolated, taken up in 100 ml. of dioxane, and assayed by the transmittance of light at 3700 Å. On the basis of the data thus obtained, it is estimated that the ratio of nitrosation in the 1-position as compared to the 3-position is 1:3.

5-Methyl-3-oximino-2-hexanone, VIIIb, was prepared by the nitrosation of 5-methyl-2-hexanone, VIIb,[14] after the manner described by Aston and Mayberry[15] in a yield of 49%. It was isolated as a yellow oil, distilling at 90–97°/2 mm., which slowly formed crystals m.p. 40–42°; reported m.p. 42°.[16]

4-Phenyl-3-oximino-2-butanone, VIIIc, was isolated in 63% crude yield, 57% yield after crystallization from ligroin, as crystals m.p. 79–80°; reported m.p. 80–81°.[17] It was prepared by the nitrosation of 4-phenyl-2-butanone, VIIc,[18] according to the procedure employed by Hartung[19] for the preparation of α-oximinopropiophenone.

4-p-Hydroxyphenyl-3-oximino-2-butanone, VIIId, was prepared by similar nitrosation of 4-*p*-hydroxyphenyl-2-butanone, VIIc[20]; after crystallization it melted at 122–126°, agreeing with the value reported by Sonn.[21]

DL-*3-Acetamido-2,4-pentanedione*, III. In a typical reduction a solution of 12.9 g. (0.1 mole) of 3-oximino, 2,4-pentanedione in 100 ml. of 98% acetic anhydride was shaken with 2 g. of A-100 catalyst[22] on a calibrated Parr apparatus with initial hydrogen pressure of 4 atmospheres. During 2 hr. 97.5% of the calculated H_2 was taken up. The catalyst was removed by filtration and the acetic anhydride–acetic acid solvent removed on a water bath at reduced pressure and at 80°. The residue was taken up in a small volume of benzene and forced out by the addition of ligroin, yielding 11.3 g. (72%); further crystallization gave white crystals m.p. 98–99°. With ferric chloride the product gave the red enol color characteristic for β-diketones. It was quite stable in boiling water.

Anal. Calcd. for $C_7H_{11}NO_3$: N, 8.92%. Found: N, 9.07, 8.94%.

DL-*3-Amino-2,4-pentanedione hydrochloride*, II, was obtained by the reduction of 3-oximino-2,4-pentandione with A-100 Pd/C catalyst according to established procedures. The product was white and crystalline, m.p. 161–162°.

Anal. Calcd. N for $C_5H_{10}NO_2Cl$; 9.24%, Found: 9.23, 9.55%.

The following were obtained by reducing the appropriate oximino ketones with catalysts of suitable potency, *i.e.*, A-100 to A-150, in ethanolic HCl as the solvent. The salts were isolated according to established procedures.

DL-*4-Methyl-3-amino-2-pentanone hydrochloride*, Xa. The salt melted with decomposition, never over more than a degree range, between 150° and 160°, depending on the rate of heating; previously reported m.p. 153.5–154°[23] and 150–151°.[24]

DL-*5-Methyl-3-amino-2-hexanone hydrochloride*, Xb. Crystals, m.p. 151–152°; previously reported 154–155°.[24]

DL-*4-Methyl-1-amino-2-pentanonehydrochloride*, XIa. Colorless crystals, m.p. (dec.) 178–180°; reported m.p. 179–180°.[13] Mixed with Xa m.p. ranged from 119° to 150°.

DL-*4-Phenyl-3-amino-2-butanone hydrochloride*, Xc. Crystals, m.p. 124–125°; previously reported m.p. 126–127°[25] and 130°.[21]

The Michael reaction with 3-acetamido-2,4-pentanedione. In a 300-ml. three-neck flask equipped with sealed stirrer, a reflux condenser, and a dropping funnel, was placed a solution of 120 ml. of absolute ethanol in which was dissolved 0.23 g. (0.01 mole) of metallic sodium. To this was added slowly and with stirring 31.4 g. (0.2 mole) of 3-acetamido-2,4-pentanedione. The solution was cooled to 0° and 17.2 g. (0.2 mole) of methyl acrylate was added at such a rate that the temperature of the reacting mixture did not rise above 10°; this required about an hour. Stirring was continued for 2 more hours and the mixture was then allowed to stand at room temperature for another day. It was then refluxed on a water bath for 2 hr. and acidified with glacial acetic acid to *p*H 6. The solvent was volatilized on a water bath at reduced pressure, leaving 31.0 g. of light oily residue, which after stirring and chilling solidified to crystals m.p. 113–114°; the product was 3-(β-carbomethoxyethyl)-3-acetamido-2,4-pentanedione, VI.

Anal. Calcd. for $C_{11}H_{17}NO_5$: N, 5.76. Found: N, 5.89, 5.80.

Ten grams of the crude product was refluxed for 2 hr. with 50 ml. of 10% HCl. After removal of the excess acid and water at reduced pressure on a water bath, the sirupy residue was taken up in a minimum of absolute ethanol; upon dilution with dry ether a salt weighing 5.5 g. (61%) was forced out; taken up in butyl alcohol and again forced out with ether, the crystals melted at 150–152°. A sample of the salt was benzoylated, forming 4-benzamido-5-ketohexanoic acid, m.p. 140–144°.

Anal. Calcd. for $C_{13}H_{15}NO_4$: N, 5.61. Found: N, 5.54, 5.46%.

3-Phthaloylglycylamino-2,4-pentanedione (IV, R = $C_6H_4(CO)_2NHCH_2$—). The procedure employed is essentially that of Johnson and Nicolet,[26] using the amino-diketone II instead of an amino acid. From 3.58 g. (0.025 mole) of 3-amino-2,4-pentanedione hydrochloride and 8.92 g. (0.025 mole) of phthaloylglycyl chloride was obtained 7.2 g. (95% of theory) of product which, crystallized from acetone-water, melted 222–225°.

(12) Analyses by Messrs. Weiler and Strauss, Oxford, England.

(13) M. Jackman, M. Klenck, B. Fishburn, B. Tullar, and S. Archer, *J. Am. Chem. Soc.*, **70**, 2886 (1948).

(14) Prepared by hydrogenating isobutyralacetone with Pd/C catalyst.

(15) J. G. Aston and M. G. Mayberry, *J. Am. Chem. Soc.*, **57**, 1888 (1935).

(16) F. Treadwell and B. Westenberger, *Ber.*, **15**, 2788 (1882).

(17) D. G. Ponzio, *Gazz. chim. ital.*, **35**, 394 (1905).

(18) Prepared by hydrogenation of benzalacetone.

(19) W. H. Hartung, *J. Am. Chem. Soc.*, **50**, 5370 (1928).

(20) Prepared by the hydrolysis of ethyl *p*-hydroxybenzylacetoacetate.

(21) A. Sonn, *Ber.*, **40**, 4666 (1907).

(22) *Cf.* W. D. Cash, F. T. Semeniuk, and W. H. Hartung, *J. Org. Chem.*, **21**, 999 (1956). The symbol A-100 designates an *acetate* palladium-on-charcoal catalyst with 100 mg. $PdCl_2$ per gram of carrier.

(23) H. Dakin and R. West, *J. Biol. Chem.*, **78**, 745, 757 (1928).

(24) H. Erlenmeyer *et al.*, *Helv. Chim. Acta*, **33**, 1221 (1950).

(25) P. A. Levene and R. E. Steiger, *J. Biol. Chem.*, **79**, 95 (1928).

(26) T. B. Johnson and B. H. Nicolet, *J. Am. Chem. Soc.*, **36**, 353 (1914).

Anal. Calcd. N for $C_{15}H_{14}N_2O_5$, 9.27%. Found: 9.18, 9.10%.

3-p-Nitrobenzoylamino-2,4-pentanedione (IV, R = *p*-$NO_2C_6H_4$—). From 5.87 g. (0.04 mole) of 3-amino-2,4-pentanedione hydrochloride and an equivalent amount of *p*-nitrobenzoyl chloride (7.7 g.) the amide was obtained in 92% yield. After crystallization from ethanol it melted 199–200°.

Anal. Calcd. N for $C_{12}H_{12}N_2O_5$: 10.61%. Found: 10.41, 10.45%.

4-Methyl-3-glycylamino-2-pentanone hydrochloride, XIIa. This compound was prepared by an adaptation of the mixed anhydride procedure for preparing amides described by Vaughan and Osato.[27] From 3.78 g. (0.025 mole) 4-methyl-3-amino-2-pentanone hydrochloride and 5.23 g. (0.025 mole) of carbobenzyloxyglycine was obtained 5.6 g. (71% of theory) of an oil which did not crystallize but did give a positive iodoform test. The crude product was subjected to hydrogenolysis with 0.5 g. of A-100 Pd/C catalyst in ethanolic HCl solvent. The product, weighing 3.5 g. (95% of theory) was a viscous hydroscopic oil which refused to crystallize even in vacuum over P_2O_5; it was insoluble in ether, gave a positive iodoform reaction, a positive test for Cl^- ion, and a positive biuret reaction. After several days evidence of decomposition could be observed. Upon benzoylation it formed a solid which, crystallized from benzene, melted 144.5–146°.

Anal. Calcd. for $C_{15}H_{20}N_2O_{30}$: N, 10.14. Found: N, 9.96, 10.18.

4-Phenyl-3-glycylamino-2-butanone hydrochloride, XIIc. From 5.97 g. (0.03 mole) of 4-phenyl-3-amino-2-butanone hydrochloride and 5.85 g. (0.03 mole) of carbobenzyloxyglycine was obtained 8.0 g. (76% of theory) 4-phenyl-3-(carbobenzyloxyglycylamino)-2-butanone, a slightly yellow solid; recrystallized from benzene-ligroin it melted 83.5–84.5°. The crystals gave a positive iodoform reaction.

Anal. Calcd. for $C_{20}H_{22}N_2O_4$: N, 7.91. Found: N, 7.82, 7.90%.

Three and a half grams of the product was subjected to hydrogenolysis with 0.5 g. of A-100 Pd/C catalyst in the presence of ethanolic HCl; the product weighed 2.5 g. (98% of calculated) and melted with decomposition at 141–142°. It was soluble in water but insoluble in ether; it gave a positive iodoform test and a positive test for the Cl^- ion. It discolored readily.

Anal. Calcd. for $C_{12}H_{17}N_2O_2Cl$: N, 10.91. Found: N 10.80, 10.77%.

Alkylation of 3-acetamido-2,4-pentandione. In a 500-ml. three-neck flask equipped with sealed stirrer, reflux condenser, and dropping funnel was placed a cold solution of 400 ml. of absolute ethanol containing 6.6 g. (0.1 mole) of sodium ethoxide and 15.7 g. (0.1 mole) of 3-acetamido-2,4-pentanedione; to the stirred solution was added over the period of an hour 13.6 g. (0.108 mole) of benzyl chloride. Stirring was continued for 4 additional hours, at which time the NaCl had separated and the reaction mixture become neutral to moist litmus. As much as possible of the solvent was removed at reduced pressure on a water bath, and to the residue was added 75 ml. of water. Two layers formed; the mixture was extracted with four 100-ml. portions of ether. Upon evaporation of the ether extracts 10.5 g. of a tan solid remained; upon recrystallization from 40% alcohol, 8.2 g. of 4-phenyl-3-acetamido-2-butanone was obtained. Further crystallization afforded product, m.p. 96.5–97°; reported m.p. 98–100°[23] and 95–95.5°.[28]

CHAPEL HILL, N. C.

(27) J. Vaughan and R. Osato, *J. Am. Chem. Soc.*, **74**, 676 (1952).

(28) G. H. Cleland and C. Niemann, *J. Am. Chem. Soc.*, **71**, 841 (1949).

[CONTRIBUTION FROM THE MERCK SHARP & DOHME RESEARCH LABORATORIES, WEST POINT, PA.]

Synthetic Antiviral Agents: II. Various Substituted 5-Oxopentanoic and 5-Oxohexanoic Acids and Certain of Their Derivatives[1]

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A number of substituted 5-oxopentanoic and 5-oxohexanoic acids, some of which showed an interesting order of antiviral activity, were prepared by the hydrolysis of the corresponding nitriles. 4,5-Diphenyl-5-oxopentanoic acid was obtained by the interaction of desoxybenzoin and β-propiolactone. 4-(*o*-Chlorophenyl)-4-phenyl-5-oxohexanoic acid was resolved through the cinchonine salt.

The intermediate 5-oxoalkanenitriles containing substituents in the 4 and/or 5 positions were produced by cyanoethylation of the appropriate ketones. 3,4-Diphenyl-5-oxohexanenitrile and 3,4,5-triphenyl-5-oxopentanenitrile were prepared by the action of cinnamonitrile on the appropriate ketone.

4-Phenyl-5-oxohexanamide was synthesized from 1-phenyl-2-propanone and acrylamide. Several derivatives, including three esters, the enol lactone and the corresponding hydroxy lactone of 4,4-diphenyl-5-oxohexanoic acid, are described.

Following the observation of antiviral properties of 4,4-diphenyl-5-oxohexanoic acid and 4-arylalkyl-4-aryl-5-oxohexanoic acids[2] a study of the properties of structurally related compounds was undertaken. There are many portions of the molecule where interesting structural variations could be made. However, it is the intent in this paper to

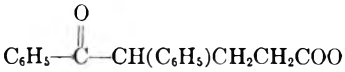
I

restrict the variations in Formula I mainly to examples where one R group is aryl, a second R is aryl, alkyl, or substituted alkyl and a third R is phenyl, methyl, or hydrogen, while the remaining R groups are hydrogen.

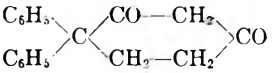
(1) A portion of the material contained in this paper was presented by the first two authors at the First Regional Meeting of the Delaware Valley Sections of the American Chemical Society, Feb. 16, 1956.

(2) E. J. Cragoe and A. M. Pietruszkiewicz, *J. Org. Chem.*, **22**, 1338 (1957).

In general, these 5-oxoalkanoic acids were prepared by the hydrolysis of the corresponding nitriles. One exception to this was the preparation of 4,5-diphenyl-5-oxopentanoic acid (II) by the action of β-propiolactone upon desoxybenzoin in the presence of potassium *tert*-butoxide. The compound



II



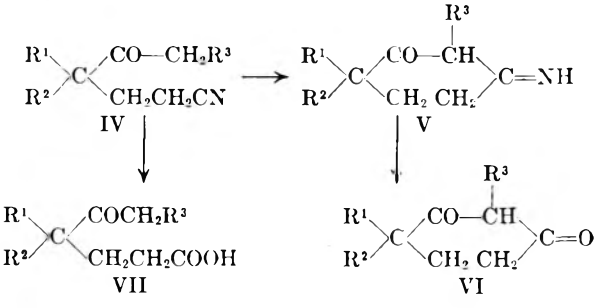
III

obtained by this method is identical with that obtained by the hydrolysis of the nitrile resulting from the monocyanoethylation of desoxybenzoin.[3] The physical properties also checked those reported by Knoevenagel[4] and by Meerwein[5] who had prepared the compound by two other methods.

Although Gresham *et al.*[6] have successfully carboxyethylated such active methylene compounds as acetoacetic ester, malonic ester, and acetylacetone by the use of β-propiolactone, the reaction had been extended to few, if any, ketones of the type considered here.

Treatment of 1,1-diphenyl-2-propanone with β-propiolactone in the presence of potassium *tert*-butoxide gave only 4,4-diphenyl-1,3-cyclohexanedione (III). From related 1,1-disubstituted-2-propanones only the corresponding 4,4-disubstituted-1,3-cyclohexanediones were isolated. The reactions leading to cyclic products will be considered in more detail in another paper.

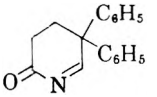
As indicated earlier,[2] hydrolysis of nitriles of the type considered here can be effected in either aqueous alkali or, preferably, by use of a sulfuric acid–acetic acid–water mixture. When the latter method was used with nitriles of type IV, cyclic by-products, V and VI, were isolated in some instances.



IV V VII VI

In fact, with 4-phenyl-4-(1-naphthylmethyl)-5-oxohexanenitrile and with 5-phenyl-5-(*o*-chlorobenzyl)-6-oxoheptanenitrile, only the cyclic compounds were isolated.

With 5-oxopentanenitriles bearing either hydrogen or an aryl group in the 5-position, obviously cyclic compounds of types V or VI cannot form. However, with 4,4-diphenyl-5-oxopentanenitrile a cyclic compound was formed in 70% yield (which has been tentatively assigned the structure represented by formula VIII) along with 13% of the anticipated 5-oxopentanoic acid. All of these cyclic products are to be considered in another paper.

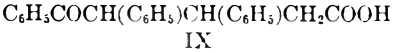


VIII

The 5-oxopentanoic and 5-oxohexanoic acids containing either one substituent or two dissimilar substituents in the 4-position have only one asymmetric carbon atom and are isolated as the racemic modification. One of the more active members of the series, 4-(*o*-chlorophenyl)-4-phenyl-5-oxohexanoic acid, was resolved through the cinchonine salt.

The hydrolysis of either 2,3- or 3,4-diphenyl-5-oxoalkanenitriles can give rise theoretically to two racemic forms of the corresponding carboxylic acids regardless of whether the nitrile is a pure racemic modification or a mixture. Thus, from the 2,3-diphenyl-5-oxohexanenitrile prepared by the method of Henecka[7] an 82% yield of a mixture of the isomers of the corresponding carboxylic acid was obtained. From this mixture there was isolated a 35% yield of a high melting racemate and 21% of a low melting racemate.

The 3,4-diphenyl-5-oxohexanenitrile used in this study was isolated from the product of the reaction of 1-phenyl-2-propanone with cinnamonitrile. This material had the melting and solubility properties of a pure compound and was assumed to be a pure racemic modification. However, hydrolysis of this material gave a product in 97% yield which appeared to be a mixture of racemates. From this mixture only one racemate was isolated in pure form (29% yield); no attempt was made to isolate another isomer.



IX

The 3,4,5-triphenyl-5-oxopentanenitrile, prepared by the reaction of desoxybenzoin and cinnamonitrile, had the melting and solubility properties of a pure compound and was assumed to be a pure racemic modification. Hydrolysis of this material gave only one racemic form of the corresponding carboxylic acid (IX). The melting point of this material corresponds to that reported for the higher melting racemate of IX, β-dehydroamaric acid. Klingemann[8] reported obtaining a mixture

(3) A. D. Campbell and I. D. R. Stevens, *J. Chem. Soc.*, 959 (1956).

(4) E. Knoevenagel, *Ber.*, **21**, 1344 (1888).

(5) H. Meerwein, *J. prakt. Chem.*, [2], **97**, 225 (1918).

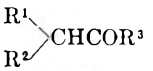
(6) T. L. Gresham, J. E. Jansen, F. W. Shaver, M. R. Fredrick, W. L. Beears, *J. Am. Chem. Soc.*, **73**, 2345 (1951).

(7) H. Henecka, *Ber.*, **82**, 104 (1949).

(8) F. Klingemann, *Ann.*, **275**, 50 (1893).

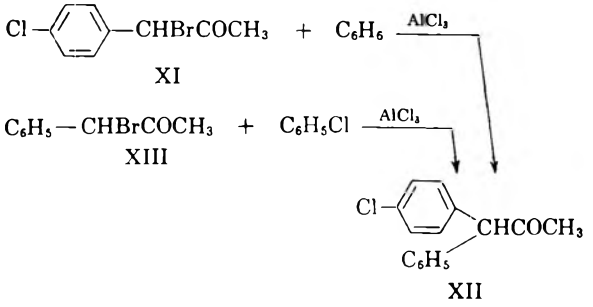
of both the high and low melting isomers by two other methods. The high melting isomer was prepared by Meerwein[5] by two still different processes.

One of the key intermediates for the synthesis of the 5-oxoalkanoic acids are the ketones of type X. These were prepared by one of several methods. Bromination of 1-phenyl-2-propanone followed by



X

a Friedel-Crafts reaction with benzene is known to give 1,1-diphenyl-2-propanone in good yields.[9] Extension of this method produced derivatives containing substituents in the aryl nucleus (R^1 and R^2 = aryl, R^3 = methyl). Interaction of 1-bromo-1-(*p*-chlorophenyl)-2-propanone (XI) with benzene gave 1-phenyl-1-(*p*-chlorophenyl)-2-propanone (XII) in 67% yield. Likewise, the reaction of 1-bromo-1-phenyl-2-propanone (XIII) with chlorobenzene gave a compound in 72% yield whose properties were identical with those of XII. Since the 2,4-dinitrophenylhydrazones prepared from each product showed no mixed melting point depression it appears that XII is produced by either method.

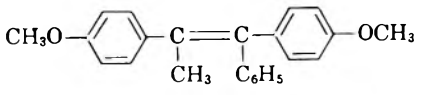


XI

XIII

XII

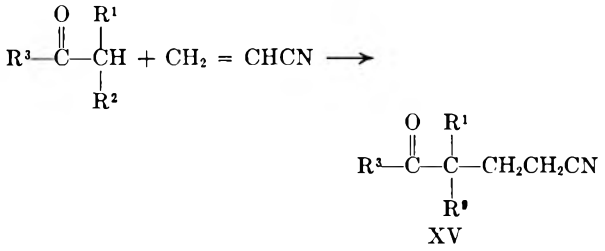
The product of the reaction of XIII with toluene was assumed to be 1-phenyl-1-(*p*-tolyl)-2-propanone. The interaction of XIII with anisole under the same conditions gave a good yield (74%) of a compound that analytical and infrared data indicate to be 1,2-bis(4-methoxyphenyl)-1-phenylpropene (XIV). This reaction is somewhat similar to that reported[10,11] for acetyl chloride and anisole with aluminum chloride which gave 1,1-bis(*p*-methoxyphenyl)ethylene.



XIV

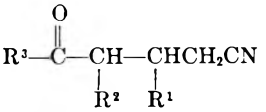
Ketones of type X, where R^2 is an alkyl or substituted alkyl radical and R^1 is aryl, were generally prepared by alkylation methods which have been described previously.[2] Special methods of synthesis were resorted to with some ketones. The details are presented in the experimental section.

The 5-oxoalkanenitriles of type XV (where R^1 = aryl or alkyl, R^2 = aryl, alkyl, or hydrogen and R^3 = CH_3, or C_2H_5) were usually prepared by cyanoethylation of the required ketone by well established procedures.[2,12] The yields were usually quite good. However, with rather hindered ketones, such as, 4-(*o*-chlorophenyl)-3-(*o*-chlorobenzyl)-2-butanone and 1-(*o*-chlorophenyl)-2-phenyl-3-pentanone, the reactions were slow and the yields were poor. With highly hindered ketones, such as, α,α-diphenylacetophenone and 1,2,3-triphenyl-1-propanone no reaction was detected.



XV

With phenylacetaldehyde the basic catalyst (benzyltrimethylammonium hydroxide) promoted violent polymerization; however, diphenylacetaldehyde gave a good yield of 4,4-diphenyl-5-oxopentanenitrile. Although generic claims for cyanoethylated arylalkylcarboxaldehydes are made in two patents[13,14] very few examples are presented.



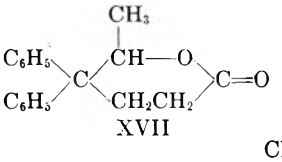
XVI

In the present study it was found that two 5-oxoalkanenitriles of type XVI where R^1 is phenyl could be synthesized by the interaction of cinnamonitrile with the appropriate ketone in the presence of a basic catalyst. With 1-phenyl-2-propanone the yield was 58% and with desoxybenzoin the yield was 80%. In the first example apparently two racemates were formed, although only one was obtained in pure form. In the second example only one racemate was found. With 1,2-diphenyl-3-butanone and cinnamonitrile little or no reaction occurred. Although the reaction of cinnamonitrile with compounds containing active methylene groups, such as fluorene, is known,[15] few examples of reactions with ketones of type X have been reported.

(9) E. M. Schultz, *Org. Syntheses*, **29**, 38 (1949).
(10) L. Gattermann, *Ber.*, **22**, 1129 (1889).
(11) L. Gattermann, R. Ehrhardt, and H. Maisch, *Ber.*, **23**, 1199 (1890).
(12) H. A. Bruson, *Org. Reactions*, **5**, 79 (1949).
(13) J. F. Walker, U. S. Patent No. **2,409,086**, Oct. 8, 1946.
(14) H. A. Bruson and T. W. Riener, U. S. Patent **2,353,687**, July 18, 1944.
(15) N. Campbell and A. E. S. Fairfull, *J. Chem. Soc.*, 1239 (1949).

The 2,3-diphenyl-5-oxohexanenitrile obtained by the Michael reaction involving benzyl cyanide and benzalacetone according to the procedure of Henecka[7] is doubtless a mixture of racemates. In any event, hydrolysis produced a mixture of two racemic carboxylic acids which have not been previously described.

Two esters, the enol lactone and the *N*-3-dimethylaminopropylamide of 4,4-diphenyl-5-oxohexanoic acid were prepared by methods already described.[2] 4,4-Diphenyl-5-hydroxyhexanoic acid lactone (XVII) was prepared by the reduction of the corresponding keto acid using Raney nickel–aluminum alloy and aqueous sodium hydroxide. Reduction of certain ketones by this method has been described by Papa *et al.*[16]



XVII

$CH_3COCH(C_6H_5)CH_2CH_2CONH_2$

XVIII

4-Phenyl-5-oxohexanamide (XVIII) was produced by the interaction of 1-phenyl-2-propanone and acrylamide in the presence of a catalyst. This reaction appears to be unique since there was no evidence of reaction between acrylamide and either acetone or 1,1-diphenyl-2-propanone.

EXPERIMENTAL[17]

Preparation of intermediates. 1-Phenyl-2-butanone was prepared in 81% yield by treatment of 1-phenyl-2-nitro-1-butene[18] with iron and hydrochloric acid.[19] *1-(o-Chlorophenyl)-2-propanone* was prepared as described earlier.[2] *1-(p-Chlorophenyl)-2-propanone* was prepared from *p*-chlorophenylacetic acid, acetic anhydride, and sodium acetate by a procedure provided by Schultz[20] which is an adaptation of the method of Magidson and Garkusha[21] for the synthesis of 1-phenyl-2-propanone. *2-Methyl-4-chloromethylthiazole* was prepared in 51% yield from 1-thioacetamido-3-chloro-2-propanone by the method of Hooper and Johnson.[22] *Diphenylacetaldehyde* was prepared from hydrobenzoin[23] by the method of Daniloff.[24] *Cinnamonitrile* was prepared by the method of Posner.[25]

The other intermediates were either commercially available or were prepared by well established procedures.

Preparation of the ketones. A. By the Friedel-Crafts method. Examples of 1,1-diaryl-2-propanones prepared from either (1) 1-bromo-1-aryl-2-propanone and benzene or from (2) 1-bromo-1-phenyl-2-propanone and a substituted benzene are presented. The anomalous reaction that occurs with (3) 1-bromo-1-phenyl-2-propanone and anisole is also described.

1. *1-(o-Chlorophenyl)-1-phenyl-2-propanone.* 1-(*o*-Chlorophenyl)-2-propanone (67 g., 0.4 mole) and benzene (250 ml.) were placed in a 1-liter, 3-necked flask equipped with a mechanical stirrer, dropping funnel, and condenser, whose open end was protected with a drying tube. The stirrer was started and bromine (64 g., 0.4 mole) was added over 15 min. The dropping funnel was replaced by a gas inlet tube and dry nitrogen admitted for 3 hr. with stirring.

A second 1-liter flask was equipped like the first one. Aluminum chloride (107.5 g., 0.8 mole) and benzene (250 ml.) were added and the mixture stirred and refluxed. The solution of brominated 1-(*o*-chlorophenyl)-2-propanone was placed in the dropping funnel and added dropwise over a period of 1 hr. The mixture was refluxed for another hour, then cooled and poured into a mixture of crushed ice (800 g.) and concd. hydrochloric acid (150 ml.).

The layers were separated and the aqueous layer extracted with ether (three 100-ml. portions). The combined organic layers were washed with water (100 ml.), 5% sodium hydroxide solution (100 ml.), and finally with water (100 ml.) again.

After drying over sodium sulfate the solvent was removed by distillation and the residue fractionally distilled at reduced pressure. The yield of material boiling at 140–145° at 0.2 mm. was 71.6 g. (74%). Refractionation gave material boiling at 142–146°/0.2 mm., m.p. 55–59°. Recrystallization from hexane and finally from petroleum ether (b.p. 30–60°) gave material melting at 62–67°.

2. *1-(p-Chlorophenyl)-1-phenyl-2-propanone.* 1-Phenyl-2-propanone (111 g., 0.83 mole) and chlorobenzene (600 ml.) were treated with bromine (135 g., 0.84 mole) in the manner described above. This solution was added to a mixture of aluminum chloride (225 g., 1.68 mole) and chlorobenzene (450 ml.). The reaction was carried out and the product isolated in the usual manner. The yield was 146.6 g. (72%), b.p. 150–156°/0.4 mm. Refractionation gave material boiling at 142–147°/0.18 mm.

The 2,4-dinitrophenylhydrazone prepared from this material and from that prepared from the product of brominated 1-(*p*-chlorophenyl)-2-propanone and benzene gave no mixed melting point depression.

3. *1,2-Bis-(p-methoxyphenyl)-1-phenylpropene.* 1-Phenyl-2-propanone (111 g., 0.83 mole) and carbon disulfide (500 g.) were treated with bromine (135 g., 0.84 mole). The solution of brominated material was added to a mixture of anisole (680 ml.) and aluminum chloride (225 g., 1.68 mole). After isolation in the usual manner the product was fractionally distilled. The yield was 204.8 g. (75%), b.p. 195–205°/0.12 mm. Refractionation followed by recrystallization from hexane and then from ethanol gave 133 g., m.p. 93–94°.

Anal. Calcd. for $C_{23}H_{22}O_2$: C, 83.60; H, 6.71; CH_3O, 18.79; mol. wt., 330.4. Found: C, 83.85; H, 6.71; CH_3O, 18.76; mol. wt. (Rast), 311 (ave.).

B. By alkylation of certain ketones: $R^1CH_2COR^3 + R^2X \rightarrow R^1CHR^2COR^3$. An example of a method employing either (1) sodium hydroxide or (2) potassium *tert*-butoxide has already been described.[2]

C. Special methods. The synthesis of *3-(o-chlorobenzyl)-4-(o-chlorophenyl)-2-butanone* was carried out by two methods: (1) by method B-2 with the appropriate reactants and (2) from the required acetoacetic ester derivative. The necessary intermediates required by method 1 and the entire synthetic sequence for method 2 are presented below.

Method 1. Ethyl 2-(o-chlorobenzyl)-3-oxobutanoate was synthesized from acetoacetic ester and *o*-chlorobenzyl chloride

(16) D. Papa, E. Schwenk, and B. Whitman, *J. Org. Chem.*, **7**, 587 (1942).

(17) All melting and boiling points are uncorrected values unless otherwise specified. Analytical data and specific rotations were supplied by K. B. Streeter and his staff.

(18) H. B. Haas, A. G. Susie, and R. L. Heider, *J. Org. Chem.*, **15**, 8 (1950).

(19) R. V. Heinzelmann, U. S. Patent **2,557,051**, June 12, 1951.

(20) E. M. Schultz, unpublished data.

(21) O. Yu. Magidson and G. A. Garkusha, *J. Gen. Chem. (U.S.S.R.)*, **11**, 339 (1941).

(22) F. E. Hooper and T. B. Johnson, *J. Am. Chem. Soc.*, **54**, 470 (1934).

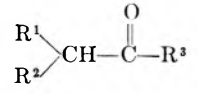
(23) S. Danilow, *Chem. Ber.*, **40**, 2390 (1927).

(24) S. Daniloff and E. Venus-Danilova, *Chem. Ber.*, **59**, 1032 (1926).

(25) T. Posner, *Ann.*, **389**, 1 (1912).

TABLE I

KETONES



No.	R^1	R^2	R^3	Synthetic Method	Yield, %	B.P., °C./Mm.	Analysis: Calcd. for	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Halogen Calcd.	Halogen Found
1	Phenyl	Phenyl	Methyl	A-1	70[a]	142–148/2.5							
2	Phenyl	*p*-Tolyl	Methyl	A-2	65	143–148/0.25	$C_{16}H_{16}O$	85.67	85.84	7.19	7.18		
3	Phenyl	*p*-Chlorophenyl	Methyl	A-1	67[b]	142–147/0.2	$C_{15}H_{13}ClO$	73.62	73.77	5.36	5.38	14.49	13.62
				A-2	72				73.21		5.59		14.75
4	Phenyl	*o*-Chlorophenyl	Methyl	A-1	74	142–146/0.2[c]	$C_{15}H_{13}ClO$	73.62	73.44	5.36	5.58		
5	Phenyl	Methyl	Methyl	B-1	77[d]	97–98/10							
												(Nitrogen)	
6	Phenyl	2-Methyl-4-thiazolylmethyl	Methyl	B-2	83[e]	144–146/0.2	$C_{14}H_{15}NOS$	68.54	68.19	6.16	6.36	5.71	5.69
7	Phenyl	2-Dimethylaminoethyl	Methyl	B-2	25[f]	83–87/0.1							
8	Phenyl	2-(2-Pyridyl)-ethyl	Methyl	[g]	39	154–158/0.1							
9	*o*-Chlorobenzyl	*o*-Chlorobenzyl	Methyl	B-2	29	163–167/0.3	$C_{17}H_{16}Cl_2O$	66.46	66.19	5.25	5.25	23.08	22.71
				C	62[h]								
10		*o*-Biphenylene	Methyl	[i]	19	M.p. 72.5–74.5							
11	Phenyl	1-Naphthylmethyl	Methyl	B-1	53[j]	177–181/0.1	$C_{20}H_{18}O$	87.55	87.51	6.61	6.47		
12	Phenyl	*o*-Chlorobenzyl	Ethyl	B-2	81[k]	169–173/0.2	$C_{17}H_{17}ClO$	74.85	74.64	6.28	6.21	13.00	13.16
13	Phenyl	Phenyl	Phenyl	[l]	78	M.p. 132–134							
14	Phenyl	Benzyl	Phenyl	B-1	82	M.p. 120–121[m]							

[a] M.p. 60–61°. Prepared by the method of Schultz.[9] [b] n_D^{25} 1.5845. [c] M.p. 62–67°. Recrystallized from petroleum ether (b.p. 30–60°). [d] Prepared by the method of Schultz and Bicking.[30] [e] n_D^{25} 1.5673. [f] Prepared by the method of Wilson[31] except that potassium *tert*-butoxide was used in place of sodamide. [g] Prepared by the method of Wilt and Levine[32] who reported a b.p. of 162–164°/2 mm. [h] n_D^{25} 1.5670. [i] There is some confusion in the literature concerning the structure and the proper synthesis of the so-called 9-acetylfluorene. It is assumed that the method of Von and Wagner,[33] which is similar to the one employed here, is valid. They reported m.p. 74.5–75.5°. [j] n_D^{25} 1.6175. [k] n_D^{25} 1.5611. [l] Prepared by the method of Robinson and Mercer.[34] Boyle *et al.*,[35] using another method, reported m.p. 135.5–136.5°. [m] Klingemann,[8] who prepared the compound by another method, reported m.p 120–121°.

TABLE II

KETONE 2,4-DINITROPHENYLHYDRAZONES

No.	R^1	R^2	R^3	M.P., °C.	Recrystallization Solvent	Calcd. for	Analysis					
							Carbon		Hydrogen		Nitrogen	
							Calcd.	Found	Calcd.	Found	Calcd.	Found
1	Methyl	Phenyl	*o*-Chlorophenyl	131 135 5	*n*-Propyl alcohol	$C_{21}H_{17}ClN_4O_4$	59.37	59.33	4.03	4.28	13.19	13.11
2	Methyl	Phenyl	*p*-Chlorophenyl	173.5–174[a]	*n*-Propyl alcohol	$C_{21}H_{17}ClN_4O_4$	59.37	59.59	4.03	3.98	13.19	13.08
				173.5–174[b]	Ethyl acetate and ethanol							
3	Methyl	Phenyl	*p*-Tolyl	176–177.5	*n* Butyl alcohol then ethyl acetate and ethanol	$C_{22}H_{20}N_4O_4$	65.33	65.38	4.98	4.97	13.86	13.83

[a] The ketone was prepared from 1-bromo-1-(*p*-chlorophenyl)-2-propanone, benzene, and aluminum chloride. *Anal.* Calcd.: Cl, 8.35. Found: Cl, 8.36. [b] The ketone was prepared from 1-bromo-1-phenyl-2-propanone, chlorobenzene, and aluminum chloride. *Anal.* Calcd.: Cl, 8.35. Found: Cl, 8.30.

according to the general method of Marvel.[26] The yield was 59%, b.p. 125–129°/0.2 mm., n_D^{25} 1.5106. Falco *et al.*[27] reported a boiling point of 172–185°/48 mm.

Anal. Calcd. for $C_{13}H_{13}ClO_3$: C, 61.30; H, 5.94; Cl, 13.92. Found: C, 61.30; H, 5.96; Cl, 13.95.

4-(o-Chlorophenyl)-2-butanone was prepared by an adaptation of the method which Leuchs *et al.*[28] used in the synthesis of a related compound.

Heating ethyl 2-(*o*-chlorobenzyl)-3-oxobutanoate (69.1 g., 0.27 mole) with acetic acid (280 ml.) and hydriodic acid (280 ml. of 58% material) gave 38 g. (78%) of product boiling at 102–108°/0.3 mm. Refractionation gave material which boiled at 98–102°/0.3 mm., n_D^{25} 1.5272.

Anal. Calcd. for $C_{10}H_{11}ClO$: C, 65.76; H, 6.07; Cl, 19.42. Found: C, 65.96; H, 6.11; Cl, 19.64.

3-(o-Chlorobenzyl)-4-(o-chlorophenyl)-2-butanone was prepared from 4-(*o*-chlorophenyl)-2-butanone and *o*-chlorobenzyl chloride according to method B-2. The yield was 29%.

Method 2. Ethyl 2,2-bis-(o-chlorobenzyl)-3-oxobutanoate was prepared by the application of the general method of Weizmann *et al.*[29] From ethyl acetoacetate (91 g., 0.7 mole), *o*-chlorobenzyl chloride (225.5 g., 1.4 mole), and powdered potassium hydroxide (92.5 g., 1.4 mole of 85% material) in acetal (425 ml.) two products were obtained. The yield of ethyl 2-(*o*-chlorobenzyl)-3-oxobutanoate was 55.6 g. (31%), b.p. 122–127°/0.2 mm. The yield of the disubstituted product was 66.1 g. (25%), b.p. 192–196°/0.2 mm., n_D^{25} 1.5593.

Anal. Calcd. for $C_{20}H_{20}ClO_3$: C, 63.33; H, 5.32. Found: C, 63.80; H, 5.44.

3-(o-Chlorobenzyl)-4-(o-chlorophenyl)-2-butanone was prepared in a manner similar to that described for 4-(*o*-chlorophenyl)-2-butanone. From ethyl 2,2-bis-(*o*-chlorobenzyl)-3-oxobutanoate (34.3 g., 0.09 mole), 58% hydriodic acid (280 ml.), and acetic acid (280 ml.) there was obtained 17.1 g. (62%) of product, b.p. 168–174°/0.3 mm. Further fractionation gave material boiling at 163–167°/0.3 mm.

A summary of the ketone syntheses appears in Table I.

The ketone 2,4-dinitrophenylhydrazones that were prepared are summarized in Table II.

Preparation of 5-oxopentanenitriles, 5-oxohexanenitriles and 5-oxoheptanenitriles. A. From a ketone or aldehyde and acrylonitrile. These syntheses were usually carried out by standard procedures.[2,13] Exceptions to the general methods are pointed out in the notes for Table III.

B. From a ketone and cinnamonitrile. Synthesis by this method is illustrated by the following example: *3,4-Diphenyl-5-oxohexanenitrile.* In a 500-ml., 3-necked flask equipped with a mechanical stirrer, dropping funnel, and thermometer was placed 1-phenyl-2-propanone (40.3 g., 0.3 mole), *tert*-butyl alcohol (125 ml.), and benzyltrimethylammonium hydroxide (6 ml. of 40% aqueous material). The stirrer was started, the solution cooled to 25°, and

(26) C. S. Marvel and F. D. Hager, *Org. Syntheses*, 2nd ed., **Coll. Vol. 1**, 248 (1941).

(27) E. A. Falco, S. DuBreuil, and G. H. Hitchings, *J. Am. Chem. Soc.*, **73**, 3758 (1951).

(28) H. Leuchs, A. Heller, and A. Hoffmann, *Ber.*, **62**, 871 (1929).

(29) Ch. Weizmann, E. Bergmann, and M. Sulzbacher, *J. Org. Chem.*, **15**, 918 (1950).

(30) E. M. Schultz and J. B. Bicking, *J. Am. Chem. Soc.*, **75**, 1128 (1953).

(31) W. Wilson, *J. Chem. Soc.*, 6 (1952).

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

(33) I. Von and E. C. Wagner, *J. Org. Chem.*, **9**, 155 (1944).

(34) R. Robinson and D. Mercer, U. S. Patent **2,298,169**, Oct. 6, 1942.

(35) J. S. W. Boyle, A. McKenzie, and W. Mitchell, *Ber.*, **70B**, 2153 (1937).

TABLE III

5-OXOPENTANENITRILES, 5-OXOHEXANENITRILES, AND 5-OXOHEPTANENITRILES

No.	Name	Synthetic Method	Yield, %	M.P., °C.	Analysis						
						Carbon		Hydrogen		Nitrogen	
					Calcd. for	Calcd.	Found	Calcd.	Found	Calcd.	Found
1	4,4-Diphenyl-5-oxopentanenitrile	A	74	80–81[a]	$C_{17}H_{15}NO$	81.90	82.21	6.06	6.19	5.62	5.59
2	4,5-Diphenyl-5-oxopentanenitrile	A	58	84–85[b]							
3	3,4,5-Triphenyl-5-oxopentanenitrile	B	80	220–221[c]	$C_{23}H_{19}NO$	84.89	84.72	5.89	5.88	4.30	4.31
4	4,4-Diphenyl-5-oxohexanenitrile	A	77	113–115[d]							
5	4-Phenyl-4-(*p*-tolyl)-5-oxohexanenitrile	A	74	96–97[e]	$C_{19}H_{19}NO$	82.28	82.16	6.90	6.73	5.05	5.06
6	4-(*p*-Chlorophenyl)-4-phenyl-5-oxohexanenitrile	A	67	92–93[f]	$C_{18}H_{16}ClNO$	72.60	72.83	5.42	5.53	4.70	4.71
7	4-(*o*-Chlorophenyl)-4-phenyl-5-oxohexanenitrile	A[g]	70	90.5–92.5[h]	$C_{18}H_{16}ClNO$	72.60	72.63	5.42	5.63	4.70	4.71
8	4-Methyl-4-phenyl-5-oxohexanenitrile	A	83	[i]							
9	4-(2-Methyl-4-thiazolylmethyl)-4-phenyl-5-oxohexanenitrile	A	94	91.5–93.5[j]	$C_{17}H_{18}N_2OS$	68.42	68.33	6.08	6.09	9.39	9.37
10	4-(2-Dimethylaminoethyl)-4-phenyl-5-oxohexanenitrile	A	75	[k]	$C_{16}H_{22}N_2O$	74.38	74.26	8.58	8.58	10.84	10.85
11	4-Phenyl-4-[2-(2-pyridyl)ethyl]-5-oxohexanenitrile	A	69	[l]	$C_{19}H_{20}N_2O$	78.05	77.77	6.90	6.79	9.58	9.51
12	4,4-Di-(*o*-chlorobenzyl)-5-oxohexanenitrile	A[g]	17	[m]	$C_{20}H_{19}Cl_2NO$	66.27	66.56	5.32	5.39	3.89	3.65
13	4-Phenyl-5-oxohexanenitrile	A	81	[n]							
14	9-Acetyl-9-(2-cyanoethyl)fluorene	A[g]	96[o]	88–90	$C_{18}H_{15}NO$	82.73	82.79	5.79	5.93	5.36	5.34
15	3,4-Diphenyl-5-oxohexanenitrile	B	68[p]	146–147.5	$C_{18}H_{17}NO$	82.09	82.06	6.51	6.43	5.32	5.30
16	2,3-Diphenyl-5-oxohexanenitrile	[q]	71								
17	4-(1-Naphthylmethyl)-4-phenyl-5-oxohexanenitrile	A	96[r]	141–143	$C_{23}H_{21}NO$	84.37	84.54	6.46	5.98	4.28	4.26
18	4-(*o*-Chlorobenzyl)-4-phenyl-5-oxoheptanenitrile	A	27	113–115[s]	$C_{20}H_{20}ClNO$	73.72	73.78	6.19	6.06	4.30	4.31

[a] Recrystallized from heptane, then from isopropyl alcohol; b.p. 162–170°/0.08 mm. [b] Recrystallized from ethyl alcohol. Campbell and Stevens[3] report a yield of 90%; m.p. 86.7–87°. [c] Recrystallized from dimethylformamide. [d] B.p. 182–183°/0.4 mm. Schultz[20] who first prepared the compound reported a m.p. of 113.5–114.5°. [e] Recrystallized from heptane and then from isopropyl alcohol; b.p. 168–174°/0.1 mm. [f] Recrystallized from isobutyl alcohol, then from ethanol and finally from heptane. B.p. 183–186°/0.1 mm. *Anal.* Calcd.: Cl, 11.91. Found: Cl, 11.88. [g] The cyanoethylation was carried out using acetonitrile instead of *tert*-butyl alcohol as a solvent. [h] Recrystallized from isopropyl alcohol; b.p. 183–185°/0.05 mm. [i] B.p. 136–140°/0.1 mm.; n_D^{25} 1.5220. This compound was first prepared by Schultz.[20] [j] Recrystallized from isopropyl alcohol; b.p. 196–202°/0.2 mm. [k] B.p. 166–170°/0.1 mm.; n_D^{25} 1.5212. [l] B.p. 195–200°/0.1 mm.; n_D^{25} 1.5612. [m] B.p. 205–210°/0.1 mm. [n] Equimolar quantities of 1-phenyl-2-propanone and acrylonitrile were used. B.p. 136–139°/0.45 mm.; n_D^{25} 1.5165; m.p. of the semicarbazone 163–164.5°. Schultz[20] prepared the compound initially and reported similar physical constants. Bergmann and Szmuszkovicz[36] reported the synthesis using sodium as a catalyst. They report a b.p. of 124–126°/0.1 mm., n_D^{25} 1.4250 (probably a typographical error) and m.p. of the semicarbazone, 163.5–165.5°. Campbell and Stevens[3] report a 64% yield using a 60–70° reaction temperature and record a b.p. of 185–190°/18 mm. [o] Recrystallized from isopropyl alcohol. [p] This is the crude yield of what is apparently a mixture of racemates. The less soluble isomer described here was recrystallized from ethanol, then acetic acid and finally from *n*-propyl alcohol; the yield was 28%. The other racemate was not isolated in pure form. [q] Prepared by the method of Henecka.[7] B.p. 178–182°/0.3 mm. [r] Recrystallized from *n*-propyl alcohol. [s] Recrystallized from isopropyl alcohol. Only one racemate was found.

TABLE IV

5-OXOPENTANOIC ACIDS AND 5-OXOHEXANOIC ACIDS

No.	Name	Synthetic Method	Yield, %	M.P., °C.	Analysis				
					Calcd. for	Carbon		Hydrogen	
						Calcd.	Found	Calcd.	Found
1	4,4-Diphenyl-5-oxopentanoic acid	A	13[a]	96–98	$C_{17}H_{16}O_3$	76.10	76.00	6.01	6.12
2	4,5-Diphenyl-5-oxopentanoic acid	A	98	134–135.5[b]	$C_{17}H_{16}O_3$	76.10	75.58	6.01	5.83
		D	19[c]						
3	3,4,5-Triphenyl-5-oxopentanoic acid	A	59[d]	242–244	$C_{23}H_{20}O_3$	80.21	80.34	5.85	5.81
4	4,4-Diphenyl-5-oxohexanoic acid	A	98[e]	137.5–139					
5	4-Phenyl-4-(*p*-tolyl)-5-oxohexanoic acid	A	97[f]	113–115	$C_{19}H_{20}O_3$	77.00	77.18	6.80	6.90
6	4-(*p*-Chlorophenyl)-4-phenyl-5-oxohexanoic acid	A	89[g]	101.5–103	$C_{18}H_{17}ClO_3$	68.24	68.39	5.41	5.44
7	4-(*o*-Chlorophenyl)-4-phenyl-5-oxohexanoic acid	A	90[h]	132–134	$C_{18}H_{17}ClO_3$	68.24	68.18	5.41	5.64
8	4-Methyl-4-phenyl-5-oxohexanoic acid	A	89	[i]	$C_{13}H_{16}O_3$	70.89	71.11	7.32	7.19
9	4-(2-Methyl-4-thiazolylmethyl)-4-phenyl-5-oxohexanoic acid	B	94[j]	137–138.5	$C_{17}H_{19}NO_3S$	64.33	64.47	6.03	5.93
10	4-(2-Dimethylaminoethyl)-4-phenyl-5-oxohexanoic acid	B	77[k]	185–187	$C_{16}H_{23}NO_3$	69.28	69.47	8.36	8.27
11	4-Phenyl-4-[2-(2-pyridyl)ethyl]-5-oxohexanoic acid	B	88[l]	171.5–173	$C_{19}H_{21}NO_3$	73.29	73.55	6.80	6.61
12	4,4-Di(*o*-chlorobenzyl)-5-oxohexanoic acid	A	100[m]	96–98	$C_{20}H_{20}Cl_2O_3$	63.33	63.58	5.32	5.27
13	4-Phenyl-5-oxohexanoic acid	A	85[n]	43–45	$C_{12}H_{14}O_3$	69.88	69.64	6.84	6.61
14	9-Acetyl-9-(2-carboxyethyl)-fluorene	A	100[o]	172–174	$C_{18}H_{16}O_3$	77.12	76.90	5.75	5.87
15	3,4-Diphenyl-5-oxohexanoic acid	A	97[p]	173–174[b]	$C_{18}H_{18}O_3$	76.57	76.65	6.43	6.46
16	2,3-Diphenyl-5-oxohexanoic acid (α form)	A	[q]	199–201	$C_{18}H_{18}O_3$	76.57	76.56	6.43	6.30
17	2,3-Diphenyl-5-oxohexanoic acid (β form)	A	[r]	167–168.5	$C_{18}H_{18}O_3$	76.57	76.37	6.43	6.19
18	*Levo* 4-(*o*-chlorophenyl)-4-phenyl-5-oxohexanoic acid	C	27	125.5–126.5[b]	$C_{18}H_{17}ClO_3$	68.24	68.19	5.41	5.43
19	*Dextro* 4-(*o*-chlorophenyl)-4-phenyl-5-oxohexanoic acid	C	44	124.5–125.5[b]	$C_{18}H_{17}ClO_3$	68.24	68.54	5.41	5.53

[a] Recrystallized from cyclohexane. A 70% yield of another compound m.p. 173–174.5° was isolated. It is believed to be 5,5-diphenyl-3,4-dihydro-2(5)pyridone. [b] Corrected melting point. [c] Recrystallized from cyclohexane. Campbell and Stevens[3] prepared the compound by hydrolysis of the corresponding nitrile using aqueous potassium hydroxide and report a yield of 90% and a m.p. of 134–135°. Knoevenagel,[4] who prepared the compound by another method, reported a m.p. of 136°. Meerwein,[5] who used still another method, reported a m.p. of 133–134°. [d] Hydrolysis of 25 g. of 3,4,5-triphenyl-5-oxopentanenitrile required refluxing for 7.5 hr. with concd. sulfuric acid (40 ml.), water (50 ml.), and acetic acid (1400 ml.). The product was recrystallized from *n*-butyl alcohol. Only one racemate was found. Klingemann,[8] who prepared the compound by another method, reported a m.p. of 240–241°. [e] Recrystallized from an acetic acid–water mixture; b.p. 194–196°/0.08 mm. This compound was first prepared by Schultz.[20] [f] Recrystallized from *n*-heptane and then from acetonitrile. [g] Recrystallized from cyclohexane and then from acetonitrile. *Anal.* Calcd.: Cl, 11.19. Found: Cl, 11.13. [h] Recrystallized from acetonitrile and then from acetic acid–water. [i] B.p. 171–174°/0.1 mm., n_D^{25} 1.5279. [j] Recrystallized from acetonitrile and then from isopropyl alcohol. *Anal.* Calcd.: N, 4.41. Found: N, 4.40. [k] Recrystallized from ethyl acetate and then from acetonitrile. *Anal.* Calcd.: N, 5.05. Found: N, 5.05. [l] Recrystallized from acetonitrile and then from ethanol. *Anal.* Calcd.: N, 4.50. Found: N, 4.54. [m] Recrystallized from heptane. *Anal.* Calcd.: Cl, 18.70. Found: Cl, 18.65. [n] B.p. 145–148°/0.2 mm. Campbell and Stevens[3] reported an 88% yield using an aqueous potassium hydroxide hydrolysis; b.p. 215–220°/18 mm.; m.p. 42°. [o] Recrystallized from acetonitrile. [p] The yield of the mixture of isomers was 97%; however, only the isomer reported here was isolated in pure form. The yield of this pure isomer was 29%. It was recrystallized from carbon tetrachloride and then from acetonitrile and finally from *n*-propyl alcohol. [q] The mixture of racemates was formed in 84% yield from which the high melting racemate (α form) was isolated in 35% yield using acetonitrile as a crystallization solvent. [r] The mixture of racemates was formed in 84% yield. From this the pure low melting racemate (β form) was isolated in 6% yield using ethyl acetate as a crystallization solvent.

cinnamonitrile (38.8 g., 0.3 mole) dissolved in *tert*-butyl alcohol (25 ml.) was added, dropwise, over a period of 30 min. A small temperature rise was noted.

The mixture was stirred and heated at 42–48° for 6 hr. More benzyltrimethylammonium hydroxide solution (1 to 2 ml.) was added every 2 hr. during the heating period so that the *p*H as measured by "Hydrion" paper remained above 10. During the reaction period a solid product slowly separated.

The solution was cooled, neutralized with dilute sulfuric acid, and the solid removed by filtration. The yield was 46 g. (58%), m.p. 141–144°. Recrystallization from alcohol, then from acetic acid, and finally from *n*-propyl alcohol gave material melting at 146–147.5°.

Table III is a summary of the nitrile syntheses.

Preparation of the 5-oxopentanoic and 5-oxohexanoic acids. These compounds were, with one exception, prepared by the hydrolysis of the corresponding nitriles. Two hydrolysis

procedures (A and B) are used; the details of the latter one are provided. The procedure (C) employed for the resolution of a racemic modification is given. Also the details of the synthesis from a ketone and β-propiolactone are included.

Table IV consists of a summary of the carboxylic acid syntheses.

A. *Hydrolysis of the nitrile using a sulfuric acid–acetic acid–water mixture.* A description of this method has already been given.[2]

B. *Hydrolysis of the corresponding nitrile using dilute sulfuric acid.* Nitriles which were acid soluble were readily hydrolyzed with 46% (by weight) sulfuric acid.

4-Phenyl-4-[2-(2-pyridyl)ethyl]-5-oxohexanoic acid. 4-Phenyl-4-[2-(2-pyridyl)ethyl]-5-oxohexanenitrile (40 g., 0.137 mole), concd. sulfuric acid (80 ml. of sp. gr. 1.84) and water (160 ml.) were refluxed for 3 hr. The solution was cooled, made strongly alkaline with 40% sodium hydroxide solution, and filtered to remove any insoluble material. The *p*H of the filtrate was adjusted to the point of minimum solubility of the product with dilute hydrochloric acid. The white solid was removed by filtration, washed with water and dried. The yield was 37.7 g. (88%). After recrystallization from acetonitrile, then from ethanol and finally again from acetonitrile, 29.9 g. remained, m.p. 171.5–173°.

C. *Resolution of a racemic 5-oxohexanoic acid. 4-(o-Chlorophenyl)-4-phenyl-5-oxohexanoic acid. Levo form.* Racemic 4-(*o*-chlorophenyl)-4-phenyl-5-oxohexanoic acid (50 g., 0.158 mole) and cinchonine (46.5 g., 0.158 mole) were dissolved in 95% ethanol (250 ml.). The solution was seeded with a few crystals of previously isolated product and refrigerated for 24 hr. The solid that separated (33.1 g.) was filtered off and dried. The mother liquor was concentrated (to 200 ml.) and refrigerated for a week. Another 6.7 g. separated, bringing the total to 39.8 g. The filtrate was concentrated (to 150 ml.), seeded, and refrigerated for a month. Another 2 g. of solid separated. This material was removed by filtration and discarded. The mother liquor was preserved for isolation of the dextro-acid. (This will be referred to as mother liquor I).

The 39.8 g. of combined products were recrystallized from 95% ethanol (250 ml.). After refrigerating for 16 hr. the yield was 28.8 g. After three more recrystallizations from ethanol, 16.1 g. remained, m.p. 171–172°.

Anal. Calcd. for $C_{18}H_{17}ClO_3 \cdot C_{19}H_{22}N_2O$: C, 72.71; H, 6.43; N, 4.58. Found: C, 73.01; H, 6.49; N, 4.54.

The above cinchonine salt (15.85 g., 0.026 mole) was suspended in water and acidified with excess hydrochloric acid. The liberated carboxylic acid was twice extracted with benzene. The combined benzene extracts were washed with water and then twice extracted with an excess of 5% sodium hydroxide solution. The aqueous solution was acidified with hydrochloric acid and extracted with benzene. The benzene solution was washed with water and dried over sodium sulfate.

Evaporation of the benzene gave 8.2 g. of the *levo*-acid. After three recrystallizations from a mixture of benzene (6 ml.) and cyclohexane (75 ml.), 6.93 g. remained; m.p. 125.5–126.5° (corr.). The $[\alpha]_D^{25}$ for a 1% solution in 95% ethanol was −59°.

Dextro form: Mother liquor I, containing the dextro acid–cinchonine salt, was evaporated at reduced pressure. The glasslike product was dissolved in acetonitrile and the insoluble material removed by filtration and discarded. The filtrate was evaporated at reduced pressure and the residue was treated with water and an excess of dilute hydrochloric acid added. The liberated carboxylic acid that separated was extracted twice with benzene. After washing with water, the benzene extract was dried over sodium sulfate.

Evaporation of the benzene gave 28.3 g. of product *A*. Recrystallization of this material from a mixture of cyclohexane (275 ml.) and benzene (60 ml.) gave 16.7 g. of product *B* which is rich in the racemic acid. Recrystallization of *B* from acetonitrile (50 ml.) gave 9.8 g. of nearly pure racemic acid *C*, m.p. 131–132°.

Concentrating and cooling the mother liquors from *B* gave 8.7 g. of *dextro* acid, m.p. 121–122°. Evaporation of the mother liquors from *C* gave 5.2 g. of the same isomer, m.p. 120–122°. These products were combined and twice recrystallized from a mixture of cyclohexane (125 ml.) and benzene (15 ml.). The final yield of *dextro* acid was 11 g., m.p. 124.5–125.5° (corr.). The $[\alpha]_D^{25}$ of a 1% solution in 95% ethanol was +59°.

D. *Interaction of a ketone and β-propiolactone. 4,5-Diphenyl-5-oxopentanoic acid.*[37] In a one-liter, 4-necked flask equipped with a mechanically driven Hershberg stirrer, thermometer, gas inlet tube, and condenser whose open end was protected with a drying tube was placed dry *tert*-butyl alcohol (450 ml.). The flask was flushed with dry nitrogen and potassium (19.5 g., 0.5 mole) added. The mixture was heated and stirred until vigorous reaction occurred, then the reaction was allowed to progress without external heating.

After all the metal had dissolved, desoxybenzoin (98 g., 0.5 mole) was added. An insoluble material immediately separated. The temperature of the stirring mixture was maintained at 40–45° while freshly distilled β-propiolactone (36 g., 0.5 mole) was added over a period of 15 min. The mixture was refluxed for 2 hr. and then the solvent was removed from the viscous product by reduced pressure distillation.

The residue was treated with water (200 ml.) and the aqueous solution extracted with benzene. (About 43% of unreacted desoxybenzoin was recovered from the benzene.) The aqueous solution was acidified with excess hydrochloric acid and the product that separated was extracted with benzene. The benzene extract was washed with water, dried over sodium sulfate, and the solvent removed by reduced pressure distillation.

The semisolid product was recrystallized from a mixture of toluene (200 ml.) and cyclohexane (600 ml.). The yield of white, crystalline product was 25 g. (19%). Two more recrystallizations gave 20 g., m.p. 134.5–135.5° (corr.). This material gave no mixed melting point depression with a sample of material prepared by the hydrolysis of 4,5-diphenyl-5-oxopentanenitrile.

Derivatives of the 5-oxohexanoic acids. Methyl 4,4-diphenyl-5-oxohexanoate. 4,4-Diphenyl-5-oxohexanoic acid (60 g., 0.21 mole) was dissolved in absolute methanol (500 ml.) and concd. sulfuric acid (17 ml.) added. The mixture was refluxed under anhydrous conditions for 5 hr. The solvent was removed by distillation at reduced pressure and the residue dissolved in benzene (200 ml.). The solution was washed with water, then with aqueous sodium bicarbonate and finally dried over sodium sulfate. Fractional distillation gave 49 g. (78%) of product b.p. 160–164°/0.15 mm. Refractionation gave 44.2 g., b.p. 165–170°/0.15 mm., n_D^{25} 1.5625.

Anal. Calcd. for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 77.00; H, 6.84.

Ethyl 4,4-diphenyl-5-oxohexanoate was prepared in a manner analogous to that described for the methyl ester. From 4,4-diphenyl-5-oxohexanoic acid (75 g., 0.27 mole), absolute ethanol (450 ml.) and concd. sulfuric acid (16 ml.) there was obtained 69 g. (84%) of product boiling at 175–178°/0.15 mm. Refractionation gave 55.9 g., b.p. 168–170°/0.15 mm.

Anal. Calcd. for $C_{20}H_{22}O_3$: C, 77.39; H, 7.15. Found: C, 77.35; H, 7.00.

4,4-Diphenyl-5-hydroxy-5-hexenoic acid lactone. 4,4-Diphenyl-5-oxohexanoic acid (42.3 g., 0.15 mole), isopropenyl acetate (45 g., 0.45 mole) and concd. sulfuric acid (3 drops) were placed in a flask equipped with a 12-in. fractionating column connected to a downward condenser. The mixture was heated so that a slow distillation occurred. About 25 ml.

(36) E. D. Bergmann and J. Szmuszkovicz, *J. Am. Chem. Soc.*, **75**, 3226 (1953).

(37) This preparation was carried out by S. C. Bell.

of material boiling at 55–59° distilled in 2.5 hr. The residue was transferred to a Claisen flask and fractionally distilled at reduced pressure. A total of 39 g. (99%) of product boiling at 170–172°/0.05 mm. was collected, m.p. 129–135°. Two recrystallizations from cyclohexane gave 35 g., m.p. 138.5–139.5°.

Anal. Calcd. for $C_{18}H_{16}O_2$: C, 81.79; H, 6.10 Found: C, 81.71; H, 6.19.

4-Phenyl-5-oxohexanamide. 1-Phenyl-2-propanone (40.3 g., 0.3 mole) was dissolved in *tert*-butyl alcohol (150 ml.) and 40% aqueous benzyltrimethylammonium hydroxide (3 ml.) were placed in a one-liter flask equipped with a mechanical stirrer and dropping funnel. A solution of acrylamide (21.3 g., 0.3 mole) dissolved in *tert*-butyl alcohol (300 ml.) was added, with stirring, over a period of 80 min. The temperature was maintained at 20–25° during the addition by external cooling.

The cooling bath was removed and more benzyltrimethylammonium hydroxide solution (12 ml.) was added. During the next 30 min. the temperature rose to 32°. Addition of a few crystals of product, obtained by evaporation of several drops of reaction mixture, initiated the separation of solid product. After stirring for another 3¾ hr. the mixture was neutralized with dilute sulfuric acid and the solid removed by filtration

The product was washed with a little *tert*-butyl alcohol and dried. The yield was 23.7 g. The solvent was removed from the combined mother liquors and washings by reduced pressure distillation. The residue was dissolved in ethyl acetate (200 ml.) and the solution dried over sodium sulfate. Evaporation of the solvent left another 12.5 g. of product, bringing the total to 36.2 g. (59%). Recrystallization first from ethanol and then from water gave material melting at 145.5–147°.

Anal. Calcd. for $C_{12}H_{15}N_2O$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.30; H, 7.45; N, 6.79.

N-(3-Dimethylaminopropyl)-4,4-diphenyl-5-oxohexanamide. 4,4-Diphenyl-5-hydroxy-5-hexenoic acid lactone (13.2 g., 0.05 mole) was placed in a small flask and treated with dry 3-dimethylaminopropylamine (5.6 g., 0.055 mole). The solid partially dissolved with the evolution of heat. The flask was fitted with a reflux condenser whose open end was protected from moisture by means of a drying tube.

The mixture was heated for 15 min. on a steam bath. The resultant solution was treated with petroleum ether (b.p. 30–60°) which caused the product to solidify. The solid was removed by filtration, washed with more petroleum ether, and dried. The yield was 17.7 g. (97%), m.p. 62–65°. One recrystallization from hexane, and then two from petroleum ether gave a product melting at 64–66°.

Anal. Calcd. for $C_{23}H_{30}N_2O_2$: C, 75.37; H, 8.25; N, 7.64. Found: C, 75.30; H, 8.15; N, 7.63.

4,4-Diphenyl-5-hydroxyhexanoic acid lactone. 4,4-Diphenyl-5-oxohexanoic acid (100 g., 0.356 mole) was dissolved in a solution of sodium hydroxide (320 g., 8 mole) and water (2500 ml.). The solution was placed in a 5-liter, 3-necked flask equipped with a mechanical stirrer, reflux condenser, thermometer, and electric heating mantle. The solution was vigorously stirred and, while maintaining the temperature at 88–92°, Raney nickel–aluminum alloy (300 g.) was added, portionwise, over 14 hr.

The mixture was filtered and the filtrate diluted with water (1 liter) and then added slowly to concd. hydrochloric acid (2 liters). The mixture was warmed for a short time and then cooled and the oil removed by decantation. The mother liquor was extracted with ethyl acetate (four 400-ml. portions). The combined extracts and oily product were dried over sodium sulfate and then the solvent removed by reduced pressure distillation.

The residual oil was treated with saturated sodium bicarbonate solution (250 ml.) and the mixture stirred and warmed. After the evolution of gas had ceased the solid that separated was removed by filtration, washed with water, and dried. [Acidification of the filtrate gave 49 g. (49%) of unreacted starting material.] The yield of crude lactone was 42.1 g. (45%), m.p. 117.5–118.5°. Recrystallization from heptane gave 41.9 g., m.p. 118–119°.

Anal. Calcd. for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 81.16; H, 6.74.

WEST POINT, PA.

[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACOLOGY, MEDICAL COLLEGE OF VIRGINIA]

meso and *dl*-2,3-Diaminosuccinic Acids[1]

HERBERT McKENNIS, JR.,[2] AND ALLAN S. YARD

Received February 6, 1958

meso and *dl*-2,3-Diaminosuccinic acids have been synthesized by hydrogenolysis of the corresponding bisbenzylamino compounds at room temperature in the presence of Pd-C and hydrogen at atmospheric pressure. The synthesis of *meso*-*N*,*N'*-dimethyl-2,3-diaminosuccinic acid was carried out in an analogous manner with platinum oxide or Pd-C (preferably the latter).

As a result of the increased use of hydrazine and its derivatives, biological attention has been focused on a number of its metabolic products.[3,4] Of these, 2,3-diaminosuccinic acid has been implicated in the metabolism of hydrazine through enzymatic reactions which are at present not completely understood. Jacobsohn and Soares[5] considered diaminosuccinic acid to result from addition of hydrazine across the double bond of fumaric acid, but did not state which diastereo or optical isomer was involved. Suzuki, Suzuki, and Egami[6] reported that *E. coli* were capable of carrying out the

(1) Presented in part at the Southwide Chemical Conference of the American Chemical Society, Memphis, Tenn., Dec. 7, 1956.

(2) Appreciation is expressed for financial aid under National Institutes of Health Grant RG 5337.

(3) A. S. Yard and H. McKennis, Jr., *Federation Proc.*, **14**, 309 (1955).

(4) A. S. Yard and H. McKennis, Jr., *J. Pharmacol. Exptl. Therap.*, **114**, 391 (1955).

(5) K. P. Jacobsohn and M. Soares, *Enzymologia*, **1**, 183 (1936–1937).

(6) S. Suzuki, N. Suzuki, and F. Egami, *J. Biochem. (Tokyo)*, **39**, 305 (1952).

reverse reaction, *i.e.*, converting *meso*-2,3-diaminosuccinic acid to fumaric acid and hydrazine. Garcia-Hernandez and Kun[7] found that *meso*-2,3-diaminosuccinic acid inhibited the transamination of aspartate and α-ketoglutarate. Shive and Macow[8] reported an anti-aspartic acid action on *E. coli*. Conveneint methods for the synthesis of the diaminosuccinic acids are, therefore, desirable.

dl-2,3-Diaminosuccinic acid has been prepared[9-13] by reduction of sodium dihydroxytartrate osazone with sodium amalgam. This laborious reduction affords a mixture of *meso* and *dl* forms. The latter was obtained only in approximately 18% yield.

Wenner[14,15] prepared *meso*-2,3-diaminosuccinic acid by reduction of *meso*-2,3-bis(benzylamino)-succinic acid in acid and obtained yields of 90% when the reduction was carried out at 800 pounds pressure and temperatures up to 60°. He also reported the reduction of *dl*-2,3-bis(benzylamino)-succinic acid under similar conditions to give the *meso*-diamino acid in unspecified yield. In the latter case the final product was identified as the dibenzoyl derivative.

The fact that *N*-debenzylations[16] can be conducted under relatively mild conditions suggested that the high pressures employed by Wenner could be avoided. Successful hydrogenolysis of *meso*-2,3-bis(benzylamino)succinic acid to *meso*-2,3-diaminosuccinic acid at room temperature and atmospheric pressure in the presence of Pd-C was then accomplished in high yield. *dl*-2,3-Bis(benzylamino) succinic acid was reduced to *dl*-2,3-diaminosuccinic acid with comparably good yields. *meso*-*N*,*N*′-Dibenzyl-*N*,*N*′-dimethyl-2,3-diaminosuccinic acid was debenzylated to yield *meso*-*N*,*N*′-dimethyl-2,3-diaminosuccinic acid under similar conditions. Thus, benzylamino acids in general appear to offer a wide range of possibilities as intermediates in the preparation of α-amino and α-*N*-methylamino acids.

The convenient intermediates, as noted by Wenner, for *meso*- and *dl*-2,3-bis(benzylamino)succinic acids are the corresponding *meso*- and *dl*-dibromosuccinic acids. *meso*-2,3-Dibromosuccinic acid is commercially available, and *dl*-2,3-dibromosuccinic acid has been previously prepared.[17] Conditions for the bromination of maleic acid to yield *dl*-dibromosuccinic acid were reinvestigated, and a procedure was developed which readily gave dibromosuccinic acid of high purity directly in much less time and without the purifications necessary in the original procedure.

After conversion of the dibromo acid to *dl*-2,3-bis(benzylamino)succinic acid, hydrogenolysis was carried out. This reduction was effected with both palladium-charcoal and platinum[15] oxide catalysts. (Use of the latter was discontinued on account of apparently variable activity of the oxide. More active samples of Adams' catalyst appreciably reduced liberated toluene to methylcyclohexane as well as effecting debenzylation.) When the reaction was carried out at room temperature, no evidence for the formation of the *meso* compound was observed. The apparently complete conversion to the *meso* acid as reported by Wenner[14] which results when higher temperatures are employed could result from epimerization of either the bisbenzylamino compound or the amino acid. Earlier workers observed the epimerization[18] of the amino acid in the presence of acid and heat. In consequence, it was considered[14] that epimerization occurred after formation of the amino acid.

Although both *meso*-2,3-diaminosuccinic acid and the *dl* compound form the usual amino acid derivatives, neither gives a positive ninhydrin reaction under conditions which are commonly employed.[19] Kuhn and Zumstein[13] reported that both compounds gave positive tests, but did not state the conditions. Garcia-Hernandez and Kun[7] reported that the *meso* compound reacted with ninhydrin, but only after strong heating.

EXPERIMENTAL[20]

meso-2,3-Diaminosuccinic acid. *meso*-2,3-Bis(benzylamino)succinic acid (10.0 g.), prepared in alcohol by the procedure of Wenner,[14] was dissolved in a mixture of 50 ml. of glacial acetic acid and 42 ml. of concentrated hydrochloric acid. Hydrogenolysis was effected at room temperature and atmospheric pressure in the presence of 1.0 g. of 10% palladium on charcoal. An equal volume of water was added, and the catalyst was removed by filtration. The filtrate was concentrated to a syrupy mass at the water pump. The residue was dissolved in dilute sodium hydroxide. Upon treatment with glacial acetic acid to *p*H 5–6, the solution deposited colorless crystals of *meso*-2,3-diaminosuccinic acid, m.p. 304° (dec.). The yield was 4.1 g. (91%). After extraction with hot water, the compound was dissolved in ammonia water. Upon boiling, the ammonia was liberated and the amino acid precipitated. For analysis the compound was dried at room temperature *in vacuo*.

Anal. Calcd. for $C_4H_8N_2O_4$: C, 32.43; H, 5.44; N, 18.91. Found: C, 32.47; H, 5.49; N, 18.95.

The melting point of the *meso* diamino acid varied considerably with the rate of heating and was not sufficiently different from the *dl* compound to be used for differentiation. The *meso* compound by the Schotten-Baumann proce-

(7) M. Garcia-Hernandez and E. Kun, *Biochem. et Biophys. Acta*, **24**, 78 (1957).

(8) W. Shive and J. Macow, *J. Biol. Chem.*, **162**, 451 (1946).

(9) J. M. Farchy and J. Tafel, *Ber.*, **26**, 1980 (1893).

(10) J. Tafel, *Ber.*, **20**, 244 (1887).

(11) J. Tafel and H. Stern, *Ber.*, **38**, 1589 (1905).

(12) T. Tamura, *J. Biochem.*, **27**, 335 (1938).

(13) R. Kuhn and F. Zumstein, *Ber.*, **58**, 1429 (1925).

(14) W. Wenner, *J. Org. Chem.*, **13**, 26 (1948).

(15) W. Wenner, U. S. Patent 2,389,099, November 13, 1945.

(16) W. H. Hartung and R. Simonoff, *Org. Reactions*, **7**, 263 (1955).

(17) A. McKenzie, *J. Chem. Soc.*, **101**, 1196 (1912).

(18) R. Kuhn and F. Zumstein, *Ber.*, **59**, 479 (1926).

(19) P. B. Hawk, B. L. Oser, and W. H. Summerson, *Practical Physiological Chemistry*, 12th Ed., The Blakiston Company, N. Y., N. Y., 1947, p. 157.

(20) Microanalyses by the Clark Microanalytical Laboratory and Spang Microanalytical Laboratory.

dure afforded a dibenzoyl derivative, m.p. 210° (dec.). This melting point, which was also dependent upon rate of heating, agrees with that reported by Wenner[14] (208–210°) and Kuhn and Zumstein[13] (212–213°). The derivative was more readily purified by solution in dilute sodium hydroxide and reprecipitation with acid than by the recrystallization from acetic acid and water employed by the previous workers.

Di-N-benzylmethylammonium meso-N,N'-dibenzyl-N,N'-dimethyl-2,3-diaminosuccinate. To a solution of 10.36 g. of *meso*-2,3-dibromosuccinic acid in 80 ml. of 95% ethanol, 40 g. of *N*-benzylmethylamine was added. The solution was refluxed for 8 hr. Upon cooling, 37.15 g. of colorless crystals of the crude dibenzylmethylammonium salt precipitated. These were collected and washed with alcohol. For analysis, the compound was recrystallized from hot ethanol, m.p. 191° (dec.), and dried at 60° and 3 mm. Hg over potassium hydroxide.

Anal. Calcd. for $C_{36}H_{46}O_4N_4$: C, 72.21; H, 7.74; N, 9.35. Found: C, 72.53; H, 7.71; N, 8.98.

meso-N,N'-Dibenzyl-N,N'-dimethyl-2,3-diaminosuccinic acid. The warm solution from the reaction (above) of benzylmethylamine and *meso*-2,3-dibromosuccinic acid was acidified to *p*H 1–2 by addition of concentrated hydrochloric acid. The solution was adjusted to *p*H 5 (hydrion paper) by addition of 10*N* sodium acetate. The cooled solution deposited a colorless product which was washed with water (7.2 g., 54%, m.p. 171°). For analysis the acid was recrystallized from warm 95% ethanol and then from warm water, m.p. 176°, and dried over potassium hydroxide at 1 mm. Hg.

Anal. Calcd. for $C_{20}H_{24}N_2O_4$: C, 67.43; H, 6.73; N, 7.86. Found: C, 67.20, H, 7.03; N, 7.58.

meso-N,N'-Dimethyl-2,3-diaminosuccinic acid. N,N'-Dibenzyl-*N,N'*-dimethyl-2,3-diaminosuccinic acid (5.15 g.) was dissolved in a mixture of 20 ml. of glacial acetic acid and 1.5 ml. of concentrated hydrochloric acid. Hydrogenolysis was conducted at atmospheric pressure and room temperature in the presence of 0.5 g. of 5% palladium on charcoal. An equal volume of water was added to dissolve the solid which separated during the reaction, and the catalyst was removed by filtration. The filtrate was adjusted to *p*H 6 by addition of sodium acetate. The methylamino acid deposited in colorless crystals (0.75 g., 29.4%, m.p. 250° dec.). For analysis the compound was recrystallized from water, m.p. 276–277° (dec.), and dried over potassium hydroxide at 3 mm. Hg. The compound is very insoluble in alcohol.

Anal. Calcd. for $C_6H_{12}O_4N_2$: C, 40.93; H, 6.82; N, 15.91. Found: C, 41.26; H, 6.85; N, 15.95.

The micromelting points (dec.) for analytical samples of the methylamino acid were 267 and 272° (rate of heating approximately one degree per minute). The decomposition of the compound, in common with other amino acids in this study, was influenced by rate of heating and particle size. The capillary melting points were similarly influenced.

dl-2,3-Dibromosuccinic acid. Bromine (19 ml.) was added to 400 ml. of dry ether[17] with cooling to keep the temperature below 25°. Powdered technical maleic acid (40 g.) was added in small portions with stirring. The temperature of the reaction mixture was kept between 18 and 25°. After washing with water and sulfurous acid, the ether solution was dried with anhydrous magnesium sulfate. Upon evaporation at room temperature in an atmosphere of dry nitrogen the solution directly afforded almost colorless crystals of *dl*-2,3-dibromosuccinic acid, m.p. 167–168°, (50–58 g.). The product was sufficiently pure for reaction with benzylamine.

dl-2,3-Bis(benzylamino)succinic acid. To a solution of 35.0 g. of *dl*-2,3-dibromosuccinic acid in 150 ml. of 95% ethanol was added cautiously, in portions, 107.5 g. of benzylamine. The mixture was heated under reflux for 5 hr. Approximately 30 ml. of ethanol was removed by vacuum distillation. The mixture solidified when cooled to room temperature. The solid mixture of benzylammonium salts was collected by suction filtration, washed with cold ethanol, and dried at room temperature. The yield was 19.6 g. of benzylammonium salts. Wenner's procedure[14] yields similar material but in our hands only after some solvent has been removed. The crystals were dissolved in a minimum volume of 2*N* potassium hydroxide. After extraction thrice with ether (125 ml. portions), the acid was precipitated by acidifying the solution with glacial acetic acid. The bisbenzylamino acid (11.1 g.) was obtained, m.p. 197–205° (dec.). For analysis the compound was recrystallized from water, dried at 60° over potassium hydroxide and 3 mm. Hg. The analytical sample melted at 188° (dec.). Although the compound was difficult to characterize by melting point, higher melting samples were generally found to be contaminated with benzylamine.

Anal. Calcd. for $C_{18}H_{20}N_2O_4$: C, 65.86; H, 6.14; N, 8.53. Found: C, 65.91; H, 6.21; N, 8.52.

dl-2,3-Diaminosuccinic acid. The *dl*-2,3-bis(benzylamino)-succinic acid (10.0 g.) was dissolved in 80 ml. of warm glacial acetic acid. Palladium on charcoal (200 mg.) was added, and the hydrogenolysis effected at room temperature and atmospheric pressure. During the course of the debenzylation the *dl*-2,3-diaminosuccinic acid precipitates. The reaction mixture was filtered with suction, and the *dl*-2,3-diaminosuccinic acid was extracted from the catalyst with 2*N* potassium hydroxide. The potassium hydroxide solution was treated with glacial acetic acid (to *p*H 5–6). The air-dried precipitate weighed 3.52 g. (75% yield, m.p. 295° dec.). For analysis the *dl* acid was purified by solution in potassium hydroxide and precipitated by acidification with glacial acetic acid, m.p. 295° (dec.). The analytical sample was washed with 95% ethanol and dried at room temperature.

Anal. Calcd. for $C_4H_6N_2O_4 \cdot H_2O$: C, 28.92; H, 6.05; N, 16.86; H_2O, 10.83. Found: C, 28.88; H, 5.87; N, 16.71; H_2O (by loss at 100° and 1 mm.) 10.43.

Dibenzoyl derivative of dl-2,3-diaminosuccinic acid. The acid yielded a dibenzoyl derivative obtained as the monohydrate.[13] The colorless crystals of the dibenzoyl derivative (113 mg.) melted at 163–176°. For analysis the compound was dissolved in a minimum quantity of 2*N* sodium hydroxide. The solution was acidified with 5*N* sulfuric acid. The precipitate was washed with water. After three reprecipitations, the product was dried over potassium hydroxide at 1 mm., m.p. 175–176°, with frothing and decomposition. Kuhn and Zumstein[13] reported the melting point at 164°. Tamura[12] reported that the same compound melted at 152°. Heating rate and particle size are possible variables.

Anal. Calcd. for $C_{18}H_{16}O_6N_2 \cdot H_2O$: C, 57.74; H, 4.85; N, 7.49. Found: C, 57.95; H, 4.84; N, 7.62.

Richmond 19, Va.

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

Stereochemistry of Cyclic Sulfides and Sulfones. Relationship to *d*-Orbital Resonance of Sulfur[1]

ROYSTON M. ROBERTS AND CHIA-CHUNG CHENG[2]

Received December 2, 1957

The theory that the failure to find the expected number of isomers of the disulfone and trisulfone of trithioacetaldehyde is attributable to the labilizing influence of two sulfonyl groups adjacent to a carbon-hydrogen bond has been tested experimentally. Two series of 4-substituted-1,3-dithiolanes have been synthesized and the members oxidized to the corresponding disulfones. In one series, each 4-substituted-1,3-dithiolane also contained a single substituent in the 2-position, so that the disulfones produced by oxidation of these compounds had two sulfonyl groups adjacent to a carbon-hydrogen bond. In the second series, each 4-substituted-1,3-dithiolane also contained *two different* substituents in the 2-position, so that the same isomerism was possible, but in the disulfones there was *not* a carbon-hydrogen bond adjacent to the two sulfonyl groups. In the latter series, two isomers of each disulfone were isolated. In the former series, no isomeric disulfones were isolated, and it was shown that the same disulfone was produced by oxidation of two isomeric 2,4-disubstituted-1,3-dithiolanes. This demonstrated clearly the significance of the carbon-hydrogen bond In the disulfones, ionization undoubtedly occurred, and the carbanion did not maintain asymmetry, so that the thermodynamically more stable of the two isomeric disulfones was isolated, regardless of which dithiolane isomer was oxidized. The stabilization of the carbanion by the adjacent sulfonyl groups is attributed to resonance involving the *d*-orbitals of sulfur.

INTRODUCTION

This research was initiated as a result of the observation by one of the authors that in the case of certain cyclic sulfones the number of stereoisomers expected on the basis of classical structural theory was not found. Although an explanation had been proposed some years earlier, there still was no direct experimental evidence to support it. This paper reports such evidence.

Trithioacetaldehyde was first prepared by Baumann and Fromm[3] and was found to exist in the form of two geometrical isomers (I and II). Later, Chattaway and Kellett[4] showed that the lower-melting isomer could be oxidized (by hydrogen peroxide followed by neutral permanganate) to a mixture of two isomeric monosulfones (III and IV) and the higher-melting isomer to a single monosulfone (V), thus establishing the geometrical structures of I and II. Baumann and Fromm oxidized the two isomers of trithioacetaldehyde separately (with potassium permanganate in sulfuric acid) and found that a single product, which melted above 340° and gave the correct analysis for a trisulfone, was obtained in each case. These products were studied by Lomnitz,[5] who found them to be identical according to all the tests that could be applied at that time. According to classical structural theory, there should be *two geometrical isomers of the trisulfone*, one corresponding in the relationships of the methyl groups to each of the trithioacetaldehyde isomers. Baumann,[6] using less oxidizing agent (acidic permanganate) prepared a disulfone from each of the trithioacetaldehyde isomers, and again the products were found to be

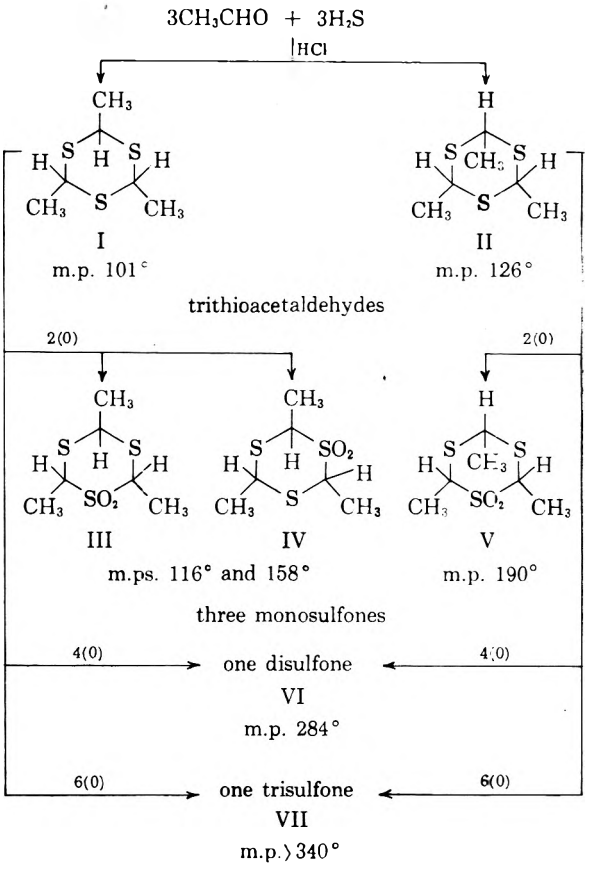


Fig. 1. Oxidation products of trithioacetaldehydes

(1) Presented at the Southwest Regional Meeting of the American Chemical Society, Houston, Tex., December 1, 1954. Taken from the M.A. thesis (1951) and the Ph.D. dissertation (1954) of C. C. Cheng, the University of Texas.

(2) Present address, Department of Chemistry, Princeton University. Recipient of an E.C.A. Scholarship from the Department of State, 1950–1953.

(3) E. Baumann and E. Fromm, *Ber.*, **22**, 2600 (1889).

(4) F. D. Chattaway and E. G. Kellett, *J. Chem. Soc.*, 1352 (1930).

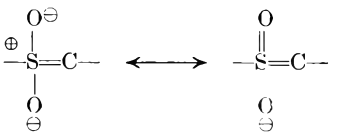
(5) E. Lomnitz, *Ber.*, **27**, 1673 (1894).

(6) E. Baumann, *Ber.*, **24**, 2074 (1893).

identical. According to classical structural theory, there should be *three geometrical isomers of the disulfone*, analogous to the three isomeric monosulfones.

Thus, in the case of the monosulfone, the expected number of isomers was found, but in the case of the disulfone and the trisulfone, less than the expected number of isomers was found. These results received notice from Richter[7] and Connor[8] independently in 1943. The explanations offered were essentially the same; in the words of the latter author, "This may be attributed to the labilizing influence of the sulfone group upon hydrogen, allowing the formation of an anion which may readily change from one geometric form to the other." It should be observed that, in the case of both the disulfone and the trisulfone, there are *two* sulfonyl groups attached to a single —$CHCH_3$— group, while this is not true of the monosulfone.

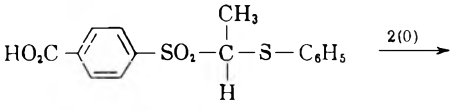
The acidifying effect of sulfonyl groups has long been known. Evidence comes from solubility in alkali solutions,[6] titration curves,[9] and hydrogen exchange with deuterium.[10] Comparison of bicyclic and acyclic trisulfones led Doering and Levy[11] to propose that resonance involving the *d*-orbitals of sulfur may contribute to the acidifying effect, and others have interpreted kinetic[12] and equilibrium[13] data as supporting the theory of *d*-orbital resonance in sulfones. Thus there is now considerable agreement that sulfur may expand its octet to a decet or dodecet, and that resonance among such hybrids as



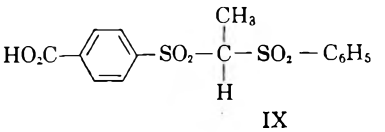
is responsible for stabilization of sulfonyl carbanions.

In the case of carbanions stabilized by carbonyl and nitro groups, a large amount of stereochemical data indicates that the carbanions do not retain optical asymmetry.[14] The stabilization of these carbanions is attributed to resonance among structures in which the original center of asymmetry has become planar. Hence, the failure of carbanions stabilized by sulfonyl groups to retain optical asymmetry may be considered as *stereochemical* support of the theory of *d*-orbital resonance.

Some information of this type has been available for many years. For example, Kipping[15] found that the monosulfone VIII could be resolved but that its oxidation to the disulfone IX produced a racemic mixture which could not be resolved. Similar di-



VIII

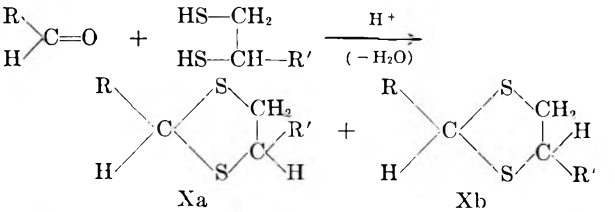


IX

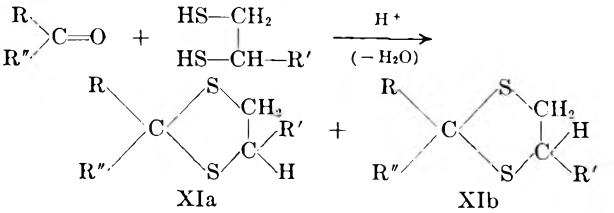
sulfones in which the sulfonyl-flanked hydrogen was replaced by an alkyl group were successfully resolved. The results from the oxidation of trithioacetaldehyde appeared to fit into the same general pattern.

DISCUSSION

The most direct way to test the theory that it is the lability of the hydrogen which is responsible for the lack of stereoisomers of trithioacetaldehyde di- and trisulfones would be to synthesize the corresponding trimers of unsymmetrical thi*cketones* and to determine the number of products obtained by oxidizing them to the di- and trisulfone stages. The authors were discouraged from this approach, however, by accounts in the literature of the frightful odor of thioketones[16] and turned to an alternate series of compounds possessing the necessary structural features and less intense odors. These were the 1,3-dithiolanes, which may be obtained from the condensation of 1,2-dithiols with carbonyl compounds. The reaction of an aldehyde or an unsymmetrical ketone with an unsymmetrical dithiol should produce two geometrically[17] isomeric 1,3-dithiolanes such as X and XI.



Xa Xb



XIa XIb

(7) G. H. Richter, *Textbook of Organic Chemistry*, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 269.

(8) R. Connor, in Gilman's *Organic Chemistry*, John Wiley and Sons, Inc., New York, N. Y., 1943, Vol. I, p. 927.

(9) E. Samén, *Arkiv Kemi, Mineral, Geol.*, **24B**, No. 6 (1947).

(10) J. Hochberg and K. F. Bonhoefer, *Z. phys. Chem.*, **184A**, 419 (1939).

(11) W. von E. Doering and L. K. Levy, *J. Am. Chem. Soc.*, **77**, 509 (1955).

(12) R. L. Heppolette and J. Miller, *J. Chem. Soc.*, 2329 (1956).

(13) H. H. Szmant and G. Suld, *J. Am. Chem. Soc.*, **76**, 3400 (1956).

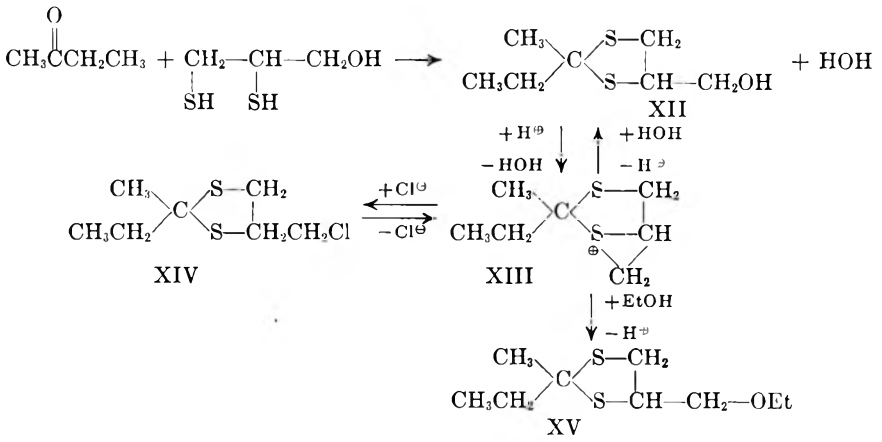
(14) See, for example, S. K. Hsü, C. K. Ingold, and C. L. Wilson, *J. Chem. Soc.*, 78 (1938); N. Kornblum, N. N. Lichtin, J. T. Patton, and D. C. Iffland, *J. Am. Chem. Soc.*, **69**, 307 (1947).

Oxidation of the isomeric 1,3-dithiolanes (X) from aldehydes would be expected to give only one disulfone because of the labile hydrogen, while oxidation of the isomeric 1,3-dithiolanes (XI) from unsymmetrical ketones would be expected to give the corresponding two isomeric disulfones, since these compounds would not contain a labile hydrogen on the carbon between the two sulfonyl groups.

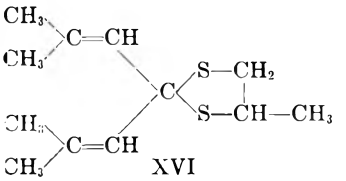
Although a number of 1,3-dithiolanes have been prepared previously, most of these were derived from symmetrical reagents, so that no isomerism was possible. The ones capable of isomerism[18,19] were all of the type X and the only one of which isomers were reported[19] had R = C_6H_5, R′ = CH_2OH. None of the corresponding sulfones have been reported.

All of the 1,3-dithiolanes which we synthesized were prepared from two dithiols, 1,2-propanedithiol and 2,3-dimercapto-1-propanol (BAL, British Anti-Lewisite). These were condensed with aldehydes and ketones to give the products listed in Tables I and II. The reaction was carried out conveniently by dissolving the carbonyl compounds and the dithiol in benzene or chloroform and passing gaseous hydrogen chloride into the mixture. In order to avoid replacing the hydroxyl group of BAL by chloride, however, it was necessary to use a modified procedure. The primary product from the condensation of BAL with carbonyl compounds is a β-thioalcohol (XII), and these are known to be extremely reactive toward nucleophilic reagents by virtue of stabilization of an intermediate cation as a sulfonium ion (XIII). Thus it was not surprising that when the condensation was effected by passing gaseous hydrogen chloride into a mixture of methyl ethyl ketone and BAL that the main product isolated was the chloromethyl compound, XIV. Water was produced in the condensation reaction and was then converted into concentrated hydrochloric acid by the hydrogen chloride.

When the chloromethyl compound XIV was treated with alkali in water-ethanol-dioxane solution, the major product was XV, resulting from alcoholysis, along with some of the hydrolysis product, XII. It was more convenient to obtain XII and the other hydroxymethyl-1,3-dithiolanes, however, by carrying out the condensation with a drop or two of concentrated hydrochloric acid as catalyst rather than by passing hydrogen chloride into the mixture.



The product from the condensation of acetone with 1,2-propanedithiol was light yellow and its carbon analysis was about 2% high. The expected product was apparently contaminated with about 13.5% of the condensation product XVI from the dithiol and phorone, formed by self-condensation of the acetone.



The 1,3-dithiolanes prepared from ketones were all liquids, despite the fact that one of them contained the undecyl group as a substituent. In only two instances was it possible to separate the isomers by distillation (Nos. 3 and 4, Table I). The compounds concerned both contained phenyl groups as substituents and the isomers had boiling points 10 to 13° apart. Apparently the flexibility of alkyl groups allows the molecules of the geometrical isomers containing them as substituents to assume very similar shapes (*e.g.*, XVII and XVIII) and hence to have very similar physical properties, but this is not true of isomers containing aryl groups (XIX and XX). Support for this explanation may be found in the properties of geometrical isomers of analogously substituted alkenes. For example, *cis*- and *trans*-3-methyl-2-pentene have

(15) F. B. Kipping, *J. Chem. Soc.*, 18 (1935).

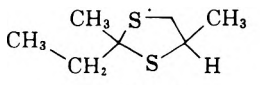
(16) E. Baumann and E. Fromm, *Ber.*, 22, 2592 (1889).

(17) It is recognized that each of the geometrical isomers actually consists of a pair of enantiomorphs, but it was not necessary for our purpose to resolve the optical isomers and no attempt was made to do so.

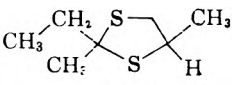
(18) L. A. Stocken, *J. Chem. Soc.*, 592 (1947).

(19) L. W. C. Miles and L. N. Owen, *J. Chem. Soc.*, 2938 (1950).

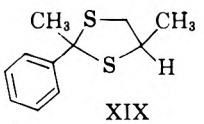
boiling points less than 3° apart, but *cis*- and *trans*-2-phenyl-2-butene boil 20° apart.[20]



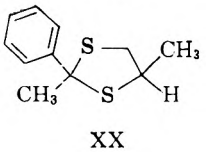
XVII



XVIII



XIX



XX

Another approach was also used to separate the isomeric 1,3-dithiolanes. The product from methyl ethyl ketone and BAL, a liquid, was converted to the 3,5-dinitrobenzoate, which was a solid, and the isomers were separated by fractional crystallization (Nos. 8A and 8B, Table I).

It was possible to separate three of the 1,3-dithiolanes prepared from aldehydes into their geometrical isomers. The product from benzaldehyde and BAL had been prepared and two isomeric forms, m.p. 89° and m.p. 90°, described previously.[19] We found it very difficult to separate the isomers by the methods used by Miles and Owen,[21] but we obtained products with melting points almost the same as those reported by them by converting the crude condensation products to the 3,5-dinitrobenzoates, separating the isomeric esters, and hydrolyzing them separately. The isomeric esters, of course, served as another pair of test compounds, and portions of each isomer were kept and oxidized separately, while the remaining portions were hydrolyzed. The condensation product from BAL and *p*-chlorobenzaldehyde was a liquid, but it was converted to the 3,5-dinitrobenzoate, which was crystalline, and the two isomers were separated by fractional crystallization.

The yields (shown in Tables I and II) were generally higher in the condensations involving ketones rather than aldehydes. (The 91% yield reported for compounds 13A and 13B in Table II refers to the preparation of the 3,5-dinitrobenzoate from the hydroxy-1,3-dithiolane, not to the condensation reaction.)

The first oxidation was carried out with potassium permanganate, but it was found that the products were more conveniently isolated and purified when hydrogen peroxide in a mixture of acetic acid and acetic anhydride was used as the oxidizing agent; this procedure was followed in all subsequent work. The 1,3-dithiolane was usually heated on a steam-cone with excess hydrogen peroxide for about 12 hr. The yields of the disulfones are given in Tables III and IV.

The oxidations of the 1,3-dithiolanes prepared from unsymmetrical ketones without exception resulted in the formation of two isomeric disulfones. One 1,3-dithiolane (No. 9, Tables I and III) prepared from a symmetrical ketone (acetone) was oxidized for comparison, and gave only one disulfone, as expected.[22] Five of the 1,3-dithiolanes from unsymmetrical ketones could not easily be separated into their isomeric forms (Nos. 1, 2, 5, 6, and 7), so the mixture of isomers was oxidized. The disulfones produced were crystalline, and were separated by fractional crystallization into the isomeric forms. The yields reported in Table III refer to the pure isomers. The 1,3-dithiolanes which could be separated into their isomeric forms (Nos. 3, 4, and 8) were oxidized separately and each gave one disulfone, as expected.

The oxidations of the 1,3-dithiolanes prepared from aldehydes without exception resulted in the formation of a single disulfone, whether mixtures of the isomeric 1,3-dithiolanes (Nos. 11, 12, and 13) or the separated isomers (Nos. 14 and 15) were oxidized. The isomeric 1,3-dithiolanes from BAL and benzaldehyde (No. 13) were separated as described previously, but were obtained in such small amounts that they were combined for the oxidation. The products from the oxidations of Nos. 11, 12, and 13 were crystallized with care and the filtrates were searched for isomers, but no evidence of their presence was found. The pure, separated isomers of 1,3-dithiolanes Nos. 14 and 15 were oxidized individually. A single product, m.p. 178–180°, was obtained by oxidation of each of the isomers of No. 14. [This compound was also obtained by treatment of the disulfone from 4-hydroxymethyl-2-phenyl-1,3-dithiolane (m.p. 159–161°) with 3,5-dinitrobenzoyl chloride.] A single product, m.p. 215–217°, was obtained by oxidation of each of the isomers of No. 15.

The fact that isomeric disulfones were obtained from oxidations of all of the 1,3-dithiolanes having two substituents in the 2-position and that isomers were not obtained from oxidations of any of the 1,3-dithiolanes having only one substituent in the 2-position indicates strongly that the lability of the hydrogen in the 2-position of the disulfones allows isomerization to the thermodynamically more stable configuration to occur in these compounds. This is demonstrated unequivocally by the

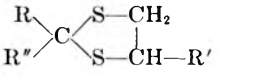
(20) D. J. Cram, *J. Am. Chem. Soc.*, **71**, 3883 (1949).

(21) The two isomers were not separated from the same reaction mixture by Miles and Owen. One was obtained by chromatography and recrystallization of the product from condensation of benzaldehyde with BAL, and the other by hydrolysis of the bromide obtained from the condensation product, after recrystallization of the bromide to constant melting point. Apparently it was not possible to obtain both isomers of either the hydroxy or bromo compounds directly by recrystallization. This was confirmed in our hands; *forty-two* systematic crystallizations failed to separate the crude condensation products. When they were converted to the 3,5-dinitrobenzoate, however, the isomers were easily separated.

(22) The small amount of disulfone to be expected from the phorone condensation product which was present as an impurity in the acetone condensation product was not detected.

TABLE I

1,3-DITHIOLANES FROM KETONES

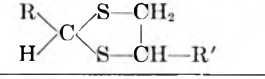


No.	R	R″	R′	Yield, %	Method[a]	B.P., °C. (mm.)	n_D^{30}	d^{30}	M.R. Calcd. (Sum.)	M.R. Found	Analyses Calcd. C	Calcd. H	Found C	Found H
1	CH_3	C_2H_5	CH_3	83	A	96–98 (25)	1.5151	1.0229	48.3	47.9	51.79	8.63	51.82	8.66
2	CH_3	n-C_3H_7	CH_3	91	A	116–117 (30)	1.5115	1.0028	52.9	52.8	54.49	9.15	54.46	9.16
3A	CH_3	C_6H_5	CH_3	24	B	135–136 (4.4)	1.5935	—	—	—	62.80	6.66	62.76	6.55
3B	CH_3	C_6H_5	CH_3	26	B	146–149 (4.4)	1.5924	—	—	—	62.80	6.66	62.60	6.53
4A	C_2H_5	C_6H_5	CH_3	19	B	112–113 (2)	1.5821	—	—	—	64.23	7.19	64.16	6.98
4B	C_2H_5	C_6H_5	CH_3	24	B	122–123 (2)	1.5811	—	—	—	64.23	7.19	64.05	7.36
5	C_2H_5	n-$C_{11}H_{23}$	CH_3	70	B	184–185 (3.5)	1.4920	—	—	—	67.48	11.33	67.20	10.91
6	CH_3	C_2H_5	CH_2Cl	76	B	82–84 (1.4)	1.5381	—	—	—	42.90	6.66	43.33	6.44
7	CH_3	C_2H_5	$CH_2OC_2H_5$	76	B, E	102–104.5 (2.8)	—	—	—	—	51.15[c]	8.59[c]	51.15	8.57
8A	CH_3	C_2H_5	CH_2ODNB[b]	—	D	94–95[e]	—	—	—	—	45.30	4.36	45.70	4.34
8B	CH_3	C_2H_5	CH_2ODNB[b]	—	D	81–82[e]	—	—	—	—	45.30	4.36	45.00	4.44
9	CH_3	CH_3	CH_3	—	B	43–45 (3.8)	1.5042	—	—	—	50.54[d]	8.24[d]	50.54	8.22
10	CH_3	C_2H_5	CH_2OH	75	C	113–116 (4.1)	1.5328	—	—	—	47.15	7.91	47.70	7.80

[a] See Exptl. section. [b] DNB = 3,5-dinitrobenzoyl. [c] Calcd. on the basis of containing 6.8% of 4-hydroxymethyl-2-ethyl-2-methyl-1,3-dithiolane (see Exptl. section). [d] Calcd. on the basis of containing 13.5% of the condensation product from phorone (see Exptl. section). [e] Melting point.

TABLE II

1,3-DITHIOLANES FROM ALDEHYDES

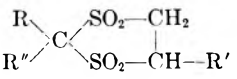


No.	R	R′	Yield, %	Method[a]	B.P., °C. (mm.) or M.P., °C.	n_D^{30}	d^{30}	M.R. Calcd. (Sum.)	M.R. Found	Analyses Calcd. C	Calcd. H	Found C	Found H
11	i-C_4H_9	CH_3	40	B	124.5–124.8 (30)	1.5119	1.0045	52.9	52.7	54.49	9.15	54.90	9.26
12	n-C_6H_{13}	CH_3	87	A	171–172 (40)	1.5030	0.9780	62.1	61.8	58.77	9.86	58.94	9.69
13A	C_6H_5	CH_2OH	56[c]	C	88.5–89.0[d]	—	—	—	—	—	—	—	—
13B	C_6H_5	CH_2OH	56[c]	C	87.5–88.0[d]	—	—	—	—	—	—	—	—
14A	C_6H_5	CH_2ODNB[b]	91[c]	D	112–113[e]	—	—	—	—	50.40	3.48[f]	50.48	3.20
14B	C_6H_5	CH_2ODNB[b]	91[c]	D	101–102[e]	—	—	—	—	50.40	3.48[g]	50.46	3.23
15A	p-ClC_6H_4	CH_2ODNB[b]	—	C, D	164–165[h]	—	—	—	—	46.31	2.97	46.10	2.93
15B	p-ClC_6H_4	CH_2ODNB[b]	—	C, D	135–137[h]	—	—	—	—	46.31	2.97	46.57	3.21

[a] See Exptl. section. [b] DNB = 3,5-dinitrobenzoyl. [c] Yield of crude mixed isomers. See Exptl. section for separation of isomers. [d] Mixture m.p., 69–75°. [e] Mixture m.p., 92–94°. [f] Calcd.: S, 15.82. Found: S, 16.01. [g] Calcd.: S, 15.82. Found: S, 16.17. [h] Mixture m.p., 135–142°.

TABLE III

1,3-DITHIOLANE DISULFONES FROM KETONES

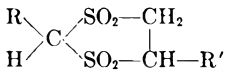


Dithiolane No.	Yield, %	Recryst. Solvent	Method[a]	M.P., °C.	Analyses Calcd. C	Calcd. H	Found C	Found H
1	13	EtOH-H_2O	F	96–97.5	37.15	6.23	37.18	5.97
	31			67–69	37.15	6.23	37.12	6.16
2	15	EtOH-H_2O	G	96–97	39.98	6.71	40.10	6.50
	30			65–66	39.98	6.71	39.97	6.56
3A	53	MeOH-H_2O	G	132.5–133.7[b]	48.20	5.12	48.70	5.22
3B	72	MeOH-H_2O	G	134.5–136.2[b]	48.20	5.12	48.00	5.18
4A	50	EtOH, 95% SKB-Bz[e]	G	134–135.5[c]	49.97	5.59	49.87	5.28
4B	42	EtOH, 95% SKB-Bz[e]	G	129–130.5[c]	49.97	5.59	49.99	5.27
5	37	EtOH-H_2O	G	74–74.5[d]	55.70	9.35	55.93	9.22
	29		G	70–71[d]	55.70	9.35	55.77	9.52
6	33	HOAc-H_2O	G	122.5–124.5	32.25	4.98	32.30	5.22
	17	EtOH-H_2O	G	104.5–106.5	32.25	4.98	32.74	4.96
7	18	EtOH-H_2O	G	173–174	40.00	6.71	40.21	6.40
	34	SKB-Bz[e]	G	149–150	40.00	6.71	40.17	6.51
8A	45	MeOH-H_2O SKB-Bz[e]	G	168.5–170.5	38.60	3.71	38.20	3.65
8B	38	MeOH-H_2O	G	110–112	38.60	3.71	39.00	3.60
9	57	EtOH-H_2O	G	124–124.5	33.94	5.70	34.30	5.79

[a] See Exptl. section. [b] Mixture m.p., 101–110°. [c] Mixture m.p., 110–127°. [d] Mixture m.p., 58–63°. [e] Skellysolve B–benzene.

TABLE IV

1,3-DITHIOLANE DISULFONES FROM ALDEHYDES



Dithiolane No.	Yield, %	Method[a]	Solvent	M.P., °C.	Analyses Calcd. C	Calcd. H	Found C	Found H
11	43	G	EtOH-H_2O	92.5–93.5	39.98	6.71	40.35	6.36
12	66	G	EtOH-H_2O	61–62	44.75	7.51	45.00	7.22
13A + 13B	43	G	—	159–161	43.46	4.38	43.75	4.52
14A[b]	72	G	EtOH	178–180[c]	43.50	3.00	44.20	2.46
							44.04	2.31
14B	61	G	EtOH	178–180[c]	—	—	—	—
15A	47	G	MeOH-H_2O	215–217[d]	—	—	—	—
15B	64	G	MeOH-H_2O	215–217[d]	40.44	2.59	40.02	2.06
							40.00	1.93

[a] See Exptl. section. [b] Calcd.: N, 5.96. Found: N, 6.10. [c] Mixture m.p., 178–180°. [d] Mixture m.p., 215–217°.

results from compounds No. 14 and 15. It is noteworthy that these isomerizations occurred in acetic acid solution at temperatures no higher than 100°.

Thus, our results with the 1,3-dithiolanes and their oxidation products are in line with those of Kipping on acyclic sulfides and sulfones, and, owing to the close analogy between the 1,3-dithiolanes and trithioacetaldehyde, there is no doubt that the stereochemistry of all of these compounds is explainable on the same basis. Apparently resonance interaction of one sulfonyl group with a carbanion is not extensive, but two adjacent carbonyl groups so strongly interact with a carbanion that it fails to retain optical asymmetry. Since this resonance interaction is thought to involve the *d*-orbitals of sulfur, the present stereochemical results provide new and definite evidence of the reality of *d*-orbital resonance in sulfones.

EXPERIMENTAL[23,24]

1,2-Propanedithiol was prepared from 1,2-dibromopropane by the method of Hagelberg[25] and Autenrieth and Wolff.[26]

(23) All melting points are corrected; boiling points are uncorrected.

2,3-Dimercapto-1-propanol (BAL) can be purchased; most of that used in this research was made from 2,3-dibromo-1-propanol, however. Potassium hydrosulfide was prepared by dissolving potassium hydroxide in methanol and saturating the cold solution with hydrogen sulfide; the dibromide was added and the reaction was allowed to proceed at room temperature in stoppered bottles for three days. The product was isolated as described previously.[27,28] Yields of 54–63% were obtained.

Preparation of 1,3-dithiolanes. Method B is illustrated by description of the synthesis of the isomeric 2,4-dimethyl-2-phenyl-1,3-dithiolanes (compounds 3A and 3B, Table I). Twenty-eight grams (0.25 mole) of 1,2-propanedithiol was mixed with 30 g. (0.25 mole) of acetophenone in 30 ml. of chloroform. Dry hydrogen chloride was passed through the mixture for three hours; heat was evolved and water separated during this time. The mixture was poured into 500 ml. of water with stirring. After allowing three hours for the layers to separate, the organic layer was removed by means of a separatory funnel. The aqueous layer was extracted once with ether and the extract was combined with the main chloroform solution, which was dried and then distilled through a 12-inch Vigreux column. After the solvents had been removed, the pressure was reduced and two fractions were collected; the first (12 g.) boiled at 131–138° (3.5 mm.) and the second (13 g.) at 145–149° (3.5 mm.). (Both of these fractions had a violet color which turned yellow after one to four days.) The combined yield was 48%. When redistilled carefully, the two fractions boiled at 134.5–136° (4.4 mm.) and 146–149° (4.4 mm.). During the redistillation it was observed that the liquid in the condenser was violet, but turned light yellow by the time it reached the receiver.[29] The refractive indices and the analyses of the isomers are given in Table I.

Benzene was used in place of chloroform as solvent in other condensations with equally good results. The product from propiophenone was easily separated into its isomers as in the example described above but none of the other products gave any indication of being separable by distillation even though an efficient column of at least ten theoretical plates was used.

Method A was identical with Method B except that no solvent was used in these early experiments. It was found later that the heat produced by the reaction was dissipated better when a solvent was used.

Method C is illustrated by the condensation of benzaldehyde with BAL; 21.2 g. of the former (redistilled) and 25 g. of the latter were dissolved in 60 ml. of anhydrous benzene. A reflux condenser was attached to the flask, and several drops of concentrated hydrochloric acid were added to the mixture through the condenser. An exothermic reaction developed, and the flask was immersed in ice water with continuous shaking. After 15 min. no more heat was produced, and the flask was heated on a steam bath for 10 min. Water separated from the reaction mixture during this time. The whole mixture was poured into 200 ml. of water and the product was extracted into chloroform. The chloroform solution was washed well with dilute sodium hydroxide solution and water, dried over magnesium sulfate, and evaporated. The crude product was recrystallized from aqueous ethanol; white needles, m.p. 68–71°, were obtained, weighing 24 g. This amounted to a yield of 56% of 4-hydroxymethyl-2-phenyl-1,3-dithiolane.

The conversion of this hydroxy compound to the ester by means of 3,5-dinitrobenzoyl chloride illustrates *Method D*. Ten grams of 4-hydroxymethyl-2-phenyl-1,3-dithiolane was mixed with 20 g. of 3,5-dinitrobenzoyl chloride in 60 ml. of dry benzene. To the mixture was added dropwise, with shaking, 40 g. of dry pyridine. The mixture was boiled on a steam bath for 25 min. with occasional shaking and then allowed to stand at room temperature overnight. To the reaction mixture was added 150 ml. of water. The organic layer was then shaken with five portions of 5% sodium bicarbonate solution, the aqueous layers being discarded. The benzene solution was then washed with water, dried over magnesium sulfate, and evaporated. The crude product was recrystallized from aqueous methanol; m.p. 91–94°, weight 18.4 g. (91%).

Anal. Calcd. for $C_{17}H_{14}N_2O_6S_2$: N, 6.91. Found: N, 7.10.

The product was crystallized fractionally from a mixture of methanol and water. Two isomers were separated. The less soluble one (Compound 14A, Table II), 8.9 g., melted at 112–113°, and the more soluble one (Compound 14B, Table II), 6.6 g., melted at 101–102°. Both were in the form of light yellow needles. The melting point of a mixture of the two was 92–94°. Analyses are reported in Table II.

The preparation of 4-ethoxymethyl-2-ethyl-2-methyl-1,3-dithiolane (Compound 7, Table I) by solvolysis of the corresponding chloromethyl compound represents *Method E*. The chloromethyl compound (8.6 g., 0.044 mole) was dissolved in a mixture of 90 ml. of dioxane and 210 ml. of 95% ethanol. Two hundred milliliters of 2*N* sodium hydroxide was added. The mixture was shaken for five minutes and allowed to stand at room temperature for 12 hr. It was then diluted with 300 ml. of water and extracted with 10-ml. portions of chloroform five times. The chloroform solution was dried over calcium chloride and distilled; 6.9 g. of colorless liquid distilled at 102.0–104.5° (2.8 mm.) and 1.2 g. of light yellow liquid distilled at 108.0–114.5° (2.8 mm.). The analysis of the main product almost corresponded to the composition of 4-ethoxymethyl-2-ethyl-2-methyl-1,3-dithiolane. The presence of 6.8% of the 4-hydroxy compound would exactly account for the analytical data; the higher-boiling product of the solvolysis was undoubtedly the 4-hydroxymethyl compound. The two products were not separated completely in the distillation.

Anal. Calcd. for 93.2% $C_9H_{18}OS_2$, 6.8% $C_7H_{14}OS_2$: C, 51.15; H, 8.59. Found: C, 51.15; H, 8.57.

Oxidation of 1,3-dithiolanes. (a) *Oxidation of the unseparated isomers of a 2,2-disubstituted-1,3-dithiolane with subsequent isolation of the two isomeric disulfones. Method F* is illustrated by the oxidation of 2-ethyl-2,4-dimethyl-1,3-dithiolane (Compound 1). This compound, 6 g. (0.037 mole) was added to a mixture of 16 g. (0.27 mole) of potassium permanganate and 15 ml. of concd. sulfuric acid in 150 ml. of water. The mixture was stirred at room temperature for 72 hr. An additional 5 g. of potassium permanganate was then added and the mixture was heated on the steam bath for 3 hr. The manganese dioxide was removed by filtration, the excess permanganate was reduced by two grams of sodium nitrite, and the acid was neutralized with potassium carbonate. A white solid separated from the solution after it had stood overnight. Systematic recrystallization from aqueous ethanol separated the isomeric sulfones, m.p. 96–97.5° and m.p. 67–69°. Analyses are given in Table III.

All of the other oxidations were carried out with hydrogen peroxide. Three examples of this, *Method G*, are given below.

(b) *Oxidation of the separated isomers of a 2,2-disubstituted-1,3-dithiolane with subsequent isolation of the two isomeric disulfones.* To a mixture of 8.7 g. of the lower-boiling

(24) Microanalyses were done by (a) Biochemical Institute, the University of Texas, Austin, Tex., (b) Clark Microanalytical Laboratory, Urbana, Ill., and (c) Drs. G. Weiler and F. B. Strauss, Oxford, England.

(25) L. Hagelberg, *Ber.*, **23**, 1085 (1890).

(26) W. Autenrieth and K. Wolff, *Ber.*, **32**, 1369 (1899).

(27) L. A. Stocken, *J. Chem. Soc.*, 592 (1947).

(28) R. A. Peters, *et al.*, U. S. Pat. **2,432,797**, Dec. 16, 1947; *Chem. Abstr.*, **42**, 2623 (1948).

(29) The violet color may be attributable to thioacetophenone, formed in small amounts by decomposition of the dithiolanes during distillation. Thioacetophenone has been reported to be a blue oil, prepared by rapid distillation of its trimer, and very unstable [E. Baumann and E. Fromm, *Ber.*, **28**, 895 (1895)].

isomer (Compound 4A) of 2-ethyl-4-methyl-2-phenyl-1,3-dithiolane in about 50 ml. of glacial acetic acid and 10 ml. of acetic anhydride was added 53 ml. of 30% hydrogen peroxide. After the heat of the initial reaction had been dissipated, the reaction mixture was heated on a steam cone for 12 hr. The solvents were removed by distillation leaving a crude crystalline product which melted at 127–129°. Three recrystallizations from 95% ethanol brought the melting point to 134.0–135.5°. Two more recrystallizations, from ethanol and then from benzene–petroleum ether, did not raise the melting point. The yield of recrystallized product was 4.5 g. (50%).

Oxidation of 8.1 g. of the higher-boiling isomer (Compound 4B) was carried out similarly. The crude product melted at 112–115°, but one recrystallization from 95% ethanol gave crystals, m.p. 129–130.5°, which differed in appearance from those from the lower-boiling isomer. A further recrystallization from benzene–petroleum ether did not raise the melting point; 4.0 g. (42%) of recrystallized product was obtained. The melting point of a mixture of the two disulfones was 110–127°. Analyses are given in Table III.

(c) *Oxidation of the unseparated isomers of a 2-monosubstituted-1,3-dithiolane with subsequent isolation of a single disulfone.* 2-Hexyl-4-methyl-1,3-dithiolane (Compound 12), 21.8 g., was dissolved in 60 ml. of glacial acetic acid and 182 g. of 30% hydrogen peroxide was added with swirling, while the flask was cooled in an ice bath. After several hours at room temperature, the reaction mixture was heated on a steam bath for 40 hr. The disulfone separated as a layer at the bottom and, after it had been separated from the upper layer, it began to crystallize. Recrystallized from aqueous alcohol, it melted at 61–62° and amounted to 19 g. (66%). Analysis is given in Table IV.

(d) *Oxidation of the separated isomers of a 2-monosubstituted-1,3-dithiolane with subsequent isolation of a single disulfone.* To a mixture of 3 g. of the high-melting isomer (Compound 14A) of 4-(3′,5′-dinitrobenzoxymethyl)-2-phenyl-1,3-dithiolane, 50 ml. of glacial acetic acid, and 10 ml. of acetic anhydride was added slowly 50 g. of 30% hydrogen peroxide. After the initial reaction had ceased, the mixture was heated on the steam bath for 12 hr. The solvents were distilled and the residue was recrystallized from ethanol to give 2.5 g. (72%) of white crystals, m.p. 178–180°.

Three grams of the lower-melting isomer (Compound 14B) was oxidized in the same manner; 2.1 g. (61%) of the same disulfone, m.p. 178–180°, was obtained. The melting point of a mixture of these two products was not depressed. Analyses are given in Table IV.

Hydrolysis of 4-(3′,5′-dinitrobenzoxymethyl)-2-phenyl-1,3-dithiolanes. Five grams of the higher-melting isomer (Compound 14A) was suspended in 200 ml. of water containing 5 g. of potassium hydroxide. The mixture was refluxed for three hours and then cooled. Crystals separated and were collected and washed with water. Recrystallization from aqueous ethanol gave 1.8 g. (70%) of white crystals, m.p. 88.5–89° (Compound 13A).

Similar treatment of 3 g. of the lower-melting isomer (Compound 14B) gave 0.85 g. (54%) of white crystals, m.p. 87.5–88° (Compound 13B). A mixture of these two products melted at 69–75°.

Oxidation of a mixture of Compounds 13A and 13B with hydrogen peroxide in acetic acid–acetic anhydride gave the disulfone, m.p. 159–161°, after recrystallization. Two grams of this disulfone was treated with 2 g. of 3,5-dinitrobenzoyl chloride in 30 ml. of dry benzene and 30 g. of dry pyridine. The mixture was stirred for 0.5 hr. and then allowed to stand at room temperature for two days. The reaction mixture was decomposed by addition of 150 ml. of water containing two grams of sodium bicarbonate. The mixture was evaporated slowly to dryness and the residue was extracted with a mixture of benzene and heptane. The crystals obtained by cooling this solution weighed 2.3 g., and melted at 178–180°. This product did not depress the melting point of the product obtained by oxidizing Compounds 14A and 14B.

AUSTIN 12, TEX.

[CONTRIBUTION FROM THE DIVISION OF PURE CHEMISTRY, NATIONAL RESEARCH COUNCIL]

Organic Deuterium Compounds. XX. Synthesis of the Deuterated Propadienes[1]

A. T. MORSE AND L. C. LEITCH

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Propadiene-d_1, -1,1-d_2, -1,3-d_2, -d_3, -d_4 and butadiene-d_6 were synthesized by dehalogenation of the appropriate halides. A few new halides and their deuterated analogs are reported. A tentative mechanism for their dehalogenation is proposed.

Several recent spectroscopic investigations have dealt with the geometry of the allene molecule.[2] Since the deuterated forms of allene were expected to provide information not obtainable by other means, syntheses were developed in this laboratory which eventually led to the preparation of all four possible deuterated allenes in moderate yields. This paper reports a number of routes to these compounds which have been rather fully explored.

Only two deuterated allenes have been reported up to now. The tetradeutero compound was isolated in small quantities from a mixture of allene-d_4 and propyne-d_4 prepared by the action of deuterium oxide on magnesium sesquicarbide, Mg_2C_3,[3] by removing the alkyne as the silver derivative.[4] An indication of the tedious nature of this process can be gained by observing that from sixty-five ml. of liquid hydrocarbons only four ml. of pure allene-d_4 was isolated. This method of preparing allene-d_4 was quite unsatisfactory for our requirements.

(1) Presented at the 132nd meeting of the American Chemical Society, New York, N. Y., September 1957. Issued as NRC No. 4808.

(2) B. P. Stoicheff, *Can. J. Phys.*, **33**, 811 (1955).

(3) L. C. Leitch and R. Renaud, *Can. J. Chem.*, **30**, 79 (1952).

(4) R. C. Lord and P. Venkateswarlu, *J. Chem. Phys.*, **20**, 1237 (1952).

Allene-1,1-d_2 was prepared in six steps very recently[5] from propyne-d_4.

Our first experiments were directed to the synthesis of allene-d_4 by the following route:

$$\underset{\text{I}}{CD_3COCD_3} \xrightarrow{PCl_5} \underset{\text{II}}{CD_3CCl_2CD_3} + \underset{\text{III}}{CD_3CCl{=}CD_2}$$

$$\underset{\text{III}}{CD_3CCl{=}CD_2} \xrightarrow[h\nu]{Cl_2} \underset{\text{IV}}{CD_2ClCCl_2CD_2Cl} \xrightarrow[EtOH]{Zn} \underset{\text{V}}{CD_2{=}C{=}CD_2}$$

Deuteroacetone, prepared from acetylene-d_2 and heavy water vapor, was further enriched in deuterium by repeated exchange with alkaline deuterium oxide. Reaction of acetone-d_6 (I) with phosphorus pentachloride gave a 30% yield of 2-chloropropene-d_5 (III) along with 42.7% of 2,2-dichloropropane-d_6 (II). It is interesting to note that in pilot runs with ordinary acetone the yields of 2-chloropropene and 2,2-dichloropropane were 47% and 25% respectively. The lower yield of 2-chloropropene-d_5 is believed to be due to an isotopic effect, the rate of proton transfer being appreciably more rapid than the rate of deuteron transfer and thereby favoring the formation of the dichloroalkane. A similar isotopic effect has been noted in the conversion of nitroethane-1,1-d_2 to acetaldehyde-d_1.[6]

Simultaneous additive and substitutive chlorination of III gave a mixture of 1,2,2,3-tetrachloropropane-d_4 (IV) and 1,1,2,2-tetrachloropropane-d_5. On dechlorination, the former led to allene-d_4 (V).

Other deuterated allenes cannot be synthesized by the route outlined above because a partly deuterated acetone such as CH_3COCD_3 rapidly equilibrates to $CH_2DCOCHD_2$ and consequently mixtures of deuterated chloropropenes would be obtained with phosphorus pentachloride. Besides, the deuterated acetone thus labelled would be rather difficult to prepare.

Several routes to the synthesis of tetrahalopropanes that would have led to other deuterated allenes on dehalogenation were explored without success. For instance, we hoped to prepare 1,2,2-tribromo-3-chloropropane-3,3-d_2 (VIII) from 1-chloro-propyne (VI)[7] by the route shown below:

$$\underset{\text{VI}}{CH_3C{\equiv}CCl} \xrightarrow{2DBr} \underset{\text{VII}}{CH_3CBr_2CD_2Cl} \xrightarrow{Br_2} \underset{\text{VIII}}{CH_2BrCBr_2CD_2Cl}$$

However (VII) could not be brominated further under ultraviolet illumination or in the presence of ferric chloride.

Another possible route to allene-1,1-d_2 was the series of reactions:

$$\underset{\text{IX}}{CH_2ClC{\equiv}CH} \xrightarrow{NaOCl} \underset{\text{X}}{CH_2ClC{\equiv}CCl} \xrightarrow{2DBr} \underset{\text{XI}}{CH_2ClCBr_2CD_2Cl}$$

A word of caution seems in order here regarding the preparation of 1,3-dichloropropyne (X). The first time this preparation was carried out a violent explosion took place in the stillhead shortly after distillation of the product had begun. Just prior to the detonation, liquid was refluxing in the stillhead at 34° C. This observation provided a clue as to the probable cause of the explosion. Small amounts of mono- or dichloroacetylene, which form dangerously explosive mixtures with air, may have been formed during the chlorination by a series of side reactions:

$$CH_2ClC{\equiv}CH \longrightarrow CH_2OHC{\equiv}CH \longrightarrow HOOCC{\equiv}CH$$

$$CCl{\equiv}CCl \longleftarrow CH{\equiv}CCl \longleftarrow HOOCC{\equiv}CCl$$

Be that as it may, in later experiments explosions were avoided by adding a little ether to the propargyl chloride. Any dichloroacetylene formed then distilled over with ether as a stable constant boiling complex.[8]

Addition of deuterium bromide to (X) evidently did not proceed as expected since the product on dehalogenation gave not allene-d_2 but allene-d_1. While this synthesis unwittingly afforded a route to the monodeuterated allene it left us without a route to the dideutero compound.

At this point further attempts to synthesize allene-1,1-d_2 and the other deuterated allenes by halogen elimination were abandoned in favor of halogen displacement using a variety of simpler and more readily available halides. This decision proved to be a fruitful one since all the deuterated allenes were subsequently prepared by this method.

From propargyl bromide, Jacobs, Teach, and Weiss[9] had obtained allene and propyne in a 2:1 ratio. In the present work allene-d_1 and propyne-3-d were obtained on dechlorinating propargyl chloride with zinc dust in deuterium oxide. 1,3-Dichloropropyne was dechlorinated to allene-1,1-d_2 and propyne-1,3-d_2. Similarly, 1,2,3,3-tetrachloropropene-1 gave allene-1,3-d_2 and propyne-1,3-d_2. Allene-d_2 and propyne-3-d_3 were obtained from 1,1,1,2,2,3,3-heptachloropropane. Finally, hexachloropropene reacted in the same way to give allene-d_4 and propyne-d_4.

Since hexachlorobutadiene-1,3 is readily available and easily dechlorinated to butadiene-1,3[10] it seemed of interest to prepare butadiene-d_6 in the same manner. The latter was obtained in 80% yield,

(5) W. E. Shuler and W. H. Fletcher, *J. Mol. Spect.*, **1**, 95 (1957).

(6) L. C. Leitch, *Can. J. Chem.*, **33**, 400, 1953.

(7) A. T. Morse and L. C. Leitch, *Can. J. Chem.*, **32**, 500 (1954).

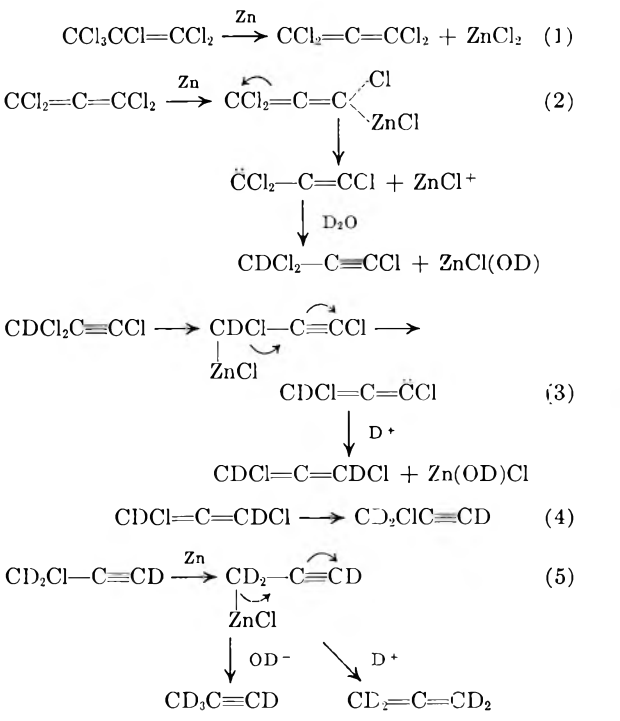
(8) E. Ott, W. Ottenmeyer, and K. Packendorf, *Ber.*, **63**, 1941 (1930).

(9) T. L. Jacobs, E. G. Teach, and D. Weiss, *J. Am. Chem. Soc.*, **77**, 6254 (1955).

(10) O. Frühwirth, *Ber.*, **74**, 1700 (1941).

thus providing in one step a highly reactive intermediate for further synthetic work.

The formation of propadiene-d_4 and propyne-d_4 can be accounted for by the mechanism outlined below:



The same mechanism would apply to the dehalogenation of propargyl chloride, 1,3-dichloropropyne, etc., but cannot, however, be invoked to explain the dechlorination of hexachlorobutadiene.

EXPERIMENTAL

Acetone-d_6. Acetylene-d_2 was prepared as described previously.[11] A mixture of deuterium oxide vapor and acetylene-d_2 in the ratio 5 to 1 was preheated to 410° and passed over a composite ZnO-FeO[12] oxide catalyst also at 410° in a bath of molten nitrates. The reaction product was condensed in a series of traps cooled with running water, acetone, and carbon dioxide at −30° and Dry Ice and acetone at −78°. The deuterium formed was oxidized over cupric oxide heated to 500° and thereby recovered as deuterium oxide. The crude product was purified by fractional distillation. The yield of deuteroacetone, b.p. 55°, was 348 grams (65%). Mass analysis indicated it was 87.4 mole % acetone-d_6, 9.4 mole % acetone-d_5, and contained in addition small amounts of less deuterated acetone.

The deuterium content was increased to 94 mole % -d_6 by repeated exchange with deuterium oxide containing a little dissolved sodium or potassium carbonate. There was little loss of acetone during the exchanges.

2,2-Dichloropropane-d_6 and 2-chloropropene-d_5. Deuteroacetone (31.0 ml.; 28.4 g.; 0.475 mole) was added dropwise to 105 g. (0.475 mole) of phosphorus pentachloride in a flask fitted with a cold finger condenser packed with Dry Ice. When reaction was complete the reaction products were distilled into a Stock trap cooled to −78° on a vacuum line.[13] On distillation through a Vigreux column, 11.7 (30.2%) of 2-chloropropene-d_5, b.p. 22–23° and 24.0 g. (42.7%) of 2,2-dichloropropane-d_6, b.p. 68–70°, were obtained. The latter contained dissolved deuterium chloride and phosphorus oxychloride which were removed by washing with two 100-ml. portions of ice cold water followed by distillation through soda-lime and then P_2O_5 on the vacuum line. The purified dichloropropane was now refractionated through a Vigreux column. A middle fraction b.p. 68.5–69.0°, n_D^{20} 1.4128, amounted to 10.8 g. For ordinary 2,2-dichloropropane, n_D^{20} is 1.4151.

Chlorination of 2-chloropropene-d_5. Chlorine was passed into a solution of 11.7 g. (0.15 mole) of 2-chloro-propene-d_5 in 15 ml. of carbon tetrachloride in a flask fitted with a cold finger condenser filled with Dry Ice. The trichloropropane-d_5 was not isolated but 15 ml. of antimony pentachloride were then added to the reaction mixture and chlorination continued at 50–70° until DCl was no longer evolved. The reaction mixture was worked up in the usual manner. The product, which was a mixture of tetrachloro- and possibly penta-chloropropanes, was fractionated in a Vigreux column under reduced pressure. The fraction b.p. 77–81°/55 mm., n_D^{20} 1.4861, was probably a mixture of 1,2,2,3- and 1,1,2,2-tetrachloropropane. The yield was 9.3 ml., 14.0 g. The pentachloropentane fraction b.p. 83–97°/55 mm., n_D^{20} 1.4920 amounted to 2.2 ml.

Propadiene-d_4. The mixed tetrachloropropanes (13.5 g.; 0.075 mole) were added dropwise from a separatory funnel to a stirred suspension of 15 g. of zinc dust in 50 ml. of ethanol in a flask fitted with a reflux condenser and a trap cooled to −78° in Dry Ice and acetone. After reaction was completed, nitrogen was swept slowly through the apparatus. The contents of the trap were distilled on the vacuum line through a U-tube containing phosphorus pentoxide. The distillate (2.5 ml.) was fractionated also on the vacuum line, collecting separately product with a vapor pressure of 46–47 mm. at −78°. Yield: 2.0 ml. of allene-d_4 measured at −78°. Mass analysis: 88.2 mole % C_3D_4, 8.85 mole % C_3D_3H.

On distillation of the zinc-ethanol residues and pouring the distillate into excess ice water, 3.0 ml. of a mixture of *cis*- and *trans*-1,2-dichloropropene-d_4 was precipitated. This volume of dichloropropene corresponds to 4.0 ml. of 1,1,2,2-tetrachlorpropene-d_2 in the original mixture dechlorinated. The yield of allene-d_4 was therefore approximately 60%.

Addition of DBr to $CH_3C{=}CCl$. 1-Chloropropyne (17.0 g., 0.24 mole) prepared as described in ref. (7) was stirred at 0° under an atmosphere of deuterium bromide. Absorption of gas ceased after 9.0 ml. of liquid deuterium bromide had been added in portions, even when the reaction mixture was warmed to room temperature. The product was freed of deuterium bromide by distilling it on the vacuum line through a U-tube filled with soda-lime. The yield of crude product was 34.0 g. (95%). It was fractionated at atmospheric pressure in a column filled with glass helices. The first fraction b.p. 103–107°, n_D^{20} 1.4894, which amounted to 4.9 ml. was probably *trans*-1-chloro-2-bromo-1-propene-1-*d*. The *cis*-fraction, b.p. 114°, n_D^{20} 1.4931 amounted to 10.2 ml.

Addition of DBr to $CH_3CBr{=}CDCl$. Fractions (1) and (2) from the preceding experiment were allowed to stand for two days in a sealed tube with 5.0 ml. of deuterium bromide. No decrease in the volume of liquid took place. On irradiating the tube with a Hanovia lamp, however, the level of liquid fell about 20 mm. in 4 hr. The reaction mixture was taken up in methylene chloride, the solution washed with water and then dried. Fractionation of the residue after distilling off the solvent gave 10.0 ml. (20.8 g.) of product b.p. 93–95°/50 mm., n_D^{20} 1.5388, which was evidently 1-chloro-2,2-dibromopropane-1-d_2, $CD_2ClCBr_2CH_3$. The pro-

(11) L. C. Leitch and A. T. Morse, *Can. J. Chem.*, **30**, 924 (1952).

(12) The composition of this catalyst is protected by several patents.

(13) A. Weissberger and N. Cheronis, *Technique of Organic Chemistry*, Vol. V, Chap. XIII, Interscience Publishers, New York, 1954, p. 375.

ton magnetic resonance spectrum of the compound showed signals only for the methyl group.

1,3-Dichloropropyne, $CH_2ClC{\equiv}CCl$. Aqueous sodium hypochlorite was prepared by passing chlorine into a solution of 102 g. of sodium hydroxide in 140 ml. of water mixed with 600 g. of crushed ice until the increase in weight was 75 g. Forty grams (0.53 mole) of propargyl chloride prepared by the method of Hatch and Chiola[14] and 10 ml. of ether were added to the solution of hypochlorite and the mixture was stirred for 3 hr. at 20°. After this time the organic layer had settled on the bottom. It was taken up in 100 ml. of ether and the aqueous layer was drawn off and extracted with the same volume of fresh ether. The combined ether extracts were washed with a little water and dried over calcium chloride. After removal of ether, the residue was fractionated under reduced pressure. The yield of 1,3-dichloropropyne, b.p. 51–52°/130 mm.; 100°/760, n_D^{20} 1.4798, was 48.5 g. (84%).

Addition of HBr to 1,3-dichloropropyne. 1,3-Dichloropropyne (16.5 ml.) was stirred under reflux for 4 hr. with 100 ml. of constant boiling hydrobromic acid. The reaction mixture was quite dark by this time and the organic layer settled on the bottom when stirring was stopped. The lower layer was taken up in methylene chloride, and worked up in the usual manner. Fractional distillation in a Vigreux column gave 8.5 ml. (27.0 g.) of product, b.p. 81–82°/14 mm., n_D^{20} 1.5730.

When this product was dehalogenated with zinc dust in ethanol 2.5 ml. of allene measured at −78° were obtained (65% yield).

Propadiene-d. Propadiene-*d* was prepared by the addition of dry propargyl chloride (22.3 g.) to a stirred, refluxing mixture of deuterium oxide (6.0 ml.), zinc dust (20 g.), and dioxane (40 ml.). The product which was collected in a spiral trap cooled to −78° amounted to 13.0 ml. Analysis for double and triple bonds indicated 20% propyne-*d* and 80% allene-*d*. Infrared analysis showed that the propyne-*d* was chiefly $CH_2DC{=}CH$ with a small amount of $CH_3C{=}CD$ also present.

Propadiene-1,1-d_2. 1,3-Dichloropropyne (25 g.) in dry dioxane (25 ml.) was added to a stirred, refluxing mixture of deuterium oxide (5.0 ml.), zinc dust (40 g.), and dioxane (125 ml.). A small portion of the halide solution was added and after 10 min. refluxing a gas began to be evolved. The remaining halide was added over 45 min. and 13 ml. of product collected in a spiral trap at −78°. Fractionation through a whirling band column separated this into three fractions.

Fraction I (1.1 ml.) distilled at −38° to −35°. Infrared analysis showed strong bands at 2940 cm.$^{-1}$ and in the 1600-cm.$^{-1}$ region again believed to be due to propylene-d_4 formed during the reaction. Mass spectral analysis gave peaks of 172.0 and 33.0 at 42 and 46 mass numbers, respectively. The latter corresponds to propylene-d_4.

Fraction II distilled at −35° to −34°. This was pure allene-d_2. The yield was 4.2 ml. (32.5% of the total). Mass spectroscopic analysis indicated the isotopic purity to be 96.2 atom % D.

Fraction III distilled at −32° to −24°, practically all being collected at the latter temperature. This was prop-1-yne-1,3-d_2 contaminated with a trace of allene-1,1-d_2. The yield was 5.5 ml. (43% of the total). Mass spectral analysis showed a deuterium content of 96.0 atom % D.

Allene-1,1-d_2 was also prepared by the addition of 1,3-dichloropropyne (40 g.) to a refluxing mixture of methanol-*d* (25 g.), dioxane (125 ml.), and zinc dust (65 g.). The product collected (16 ml.) was treated with aqueous potassium mercuric oxide to remove the propyne-d_2 present. Analysis by mass spectrometer upon the remaining sample (9.5 ml.; 60% of the total) gave an isotopic purity of 90.0 atom % D and showed a trace of propylene-d_4 present as an impurity indicated by a peak at 46 mass numbers. The methanol-*d* used in this preparation had a lower deuterium content than the heavy water used above, hence the reason for the allene-1,1-d_2 showing a poorer analysis.

Propadiene-1,3-d_2. 1,2,3,3-Tetrachloropropene-1 (63 g., 0.35 mole), prepared according to Heilbron[15] in dioxane (25 ml.) was added to a mixture of methanol-*d* (23 g.), zinc dust (75 g.), and dioxane (250 ml.) in the same manner as described previously. The product which was collected (18 ml.) was separated into three fractions.

Fraction I (1.5 ml.) distilled at −37° to −34.5° and contained the usual amount of propylene-d_4 as an impurity.

Fraction II was allene-1,3-d_2 and distilled at −34.5° to −34°. The yield was 11.0 ml. (60% of the total). Mass spectrometric analysis showed 87.0 atom % D.

Fraction III (2.5 ml.) was a mixture of prop-1-yne-3,3-d_2 and prop-1-yne-1,3-d_2 with the latter predominating as indicated by the infrared spectrum.

Propadiene-d_3. Addition of *unsym*-heptachloropropane (75 g.; 0.27 mole) in dioxane (20 ml.) to a mixture of deuterium oxide (5.0 ml.), zinc dust (110 g.), and dioxane (300 ml.) gave 11.0 ml. of product measured at −78°. Three fractions were obtained on distillation.

Fraction I (10 ml.) was allene-d_3 contaminated with propylene-d_5.

Fraction II was allene-d_3. This distilled at −35° to −34° and amounted to 4.0 ml. (36.5% of the total). Mass spectrometric analysis gave a deuterium content of 97.6 atom % D.

Fraction III was a mixture of prop-1-yne-3,3,3-d_3 and prop-1-yne-1,3,3-d_3 with the latter predominating. The yield was 3.6 ml. (33% of the total) Mass spectrometric analysis indicated 97.3 atom % D.

Propadiene-d_4 and propyne-d_4. Hexachloropropene was obtained from Columbia Chemicals Limited, Columbia, S. C.

In a 1-l. three-necked, round-bottomed flask with a dropping funnel, a magnetic stirrer, and a reflux condenser to which was connected a spiral trap cooled to −78° with Dry Ice and acetone were added 600 ml. of anhydrous dioxane (purified by distillation over sodium), 42.0 ml. of 99.8% deuterium oxide, and 200 g. of zinc dust. When the stirred mixture had refluxed gently for 20 min. to 0.5 hr., addition of 83.0 g. (50.0 ml.) of hexachloropropene was begun and completed in 1.5 hr. Stirring was continued for another half hour and the apparatus was flushed with a slow stream of dry nitrogen. The yield of propadiene-d_4 and propyne-d_4 mixture varied between 15.0 and 18.0 ml. of liquid measured at −78° (68 to 80% of the theoretical amount) after distillation on the vacuum line.

The mixture was separated in a column with a whirling band. The propadiene-d_4 and propyne-d_4 mixture was distilled on vacuum line into a 25-ml. thermally insulated still-pot which was then attached to the distilling column. The head of the column was cooled by circulating through it pentane cooled in liquid nitrogen. Fractions were collected in a spiral trap cooled to −78°. From 18.0 ml. of liquid hydrocarbons there was obtained 11.3 ml. of propadiene-d_4, b.p. −34 to −32° and 4.8 ml. of propyne-d_4 contaminated with a little propadiene-d_4.

The yield of propadiene-d_4 is thus approximately 40%. The infrared spectrum showed only a faint band due to acetylenic hydrogen (or deuterium).

Butadiene-d_6. Hexachlorobutadiene was obtained from Columbia Chemicals, Columbia, S. C. Dechlorination of hexachlorobutadiene was carried out essentially as described for the lower halide. From 230 g. of anhydrous dioxane, 85 g. of zinc dust, 30 ml. of 99.8% deuterium oxide, and 65 g. (0.25 mole) of hexachlorobutadiene there was obtained 12.0 ml. of butadiene-d_6 measured at −60°. Its vapor pressure at −30° was nearly constant. The yield was 80%

(14) L. F. Hatch and V. Chiola, *J. Am. Chem. Soc.*, **73**, 360 (1951).

(15) I. M. Heilbron, R. N. Hislop, and F. Irving, *J. Chem. Soc.*, 782 (1936).

of the theoretical amount. A mass analysis of an aliquot gave the following figures:

Mass	Mass Peak
60	375.97
59	32.53
58	174.41
57	13.36
56	44.4
55	2.85

The isotopic purity is thus 92.3 mole % C_4D_6.

Acknowledgment. The authors wish to thank Dr. F. P. Lossing and Mrs. F. Kutschke for the mass analyses, Dr. H. J. Bernstein for an NMR spectrum, Dr. B. P. Stoicheff for several infrared spectra, and Mr. D. Kovachic for assistance in preparing propadiene-d_4. Special thanks are due to Mr. D. J. Kennedy of Shawinigan Chemicals, Ltd. for the use of their laboratory facilities in the preparation of acetone-d_6.

OTTAWA, CAN.

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

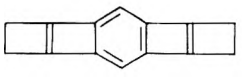
Identification of Lagidze's Hydrocarbon

STUART W. FENTON, WILLIAM N. LIPSCOMB, MICHAEL G. ROSSMANN, AND JAMES H. OSBORN

Received January 17, 1958

The hydrocarbon obtained by the reaction of 2-butyne-1,4-diol diacetate and benzene in the presence of aluminum chloride has been identified as 2-phenylnaphthalene. Acetophenone and 2-acetyl-5,6,7,8-tetrahydronaphthalene were also isolated.

The reaction of 2-butyne-1,4-diol diacetate with benzene in the presence of aluminum chloride has been described by Lagidze and Petrov.[1] Two of the products isolated were assigned molecular formulas $C_{14}H_{10}$ and $C_{12}H_{14}O$, on the basis of elemental analysis and molecular weights. These authors suggested that these compounds had structures (I) and (II), respectively.



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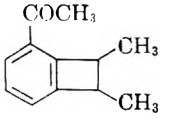


II

Although little degradative evidence was advanced in support of these formulations, the physical and analytical data were difficult to dismiss, particularly for the hydrocarbon. This substance was isomeric with phenanthrene and melted within 2° of that compound. However, a mixture melting point with phenanthrene showed a considerable depression. An x-ray crystallographic examination placed this substance in space group $P2_1/a$ with two molecules in the unit cell. In the absence of orientational disorder in the crystal, this information is very strong evidence that the molecule has a center of symmetry. While the data did not establish (I) as the structure for the hydrocarbon, other structural possibilities meeting these specifications appear equally improbable. A reinvestigation of the products of this reaction seemed indicated.

(1) R. M. Lagidze and A. D. Petrov, *Doklady Akad. Nauk. S.S.S.R.*, **83**, 235 (1952).

A mixture of freshly sublimed aluminum chloride and 2-butyne-1,4-diol diacetate in a molar ratio of approximately 2.5 : 1 was heated at the reflux temperature with excess benzene for six hours. After the lower boiling products had been removed by distillation, a colorless crystalline solid was separated from the viscous residue by sublimation. This solid was established to be Lagidze's hydrocarbon by comparisons of its physical properties with those described.[1] These results are shown in Table I.

TABLE I

COMPARISON OF CRYSTALLOGRAPHIC DATA

	This Study	Lagidze & Petrov
M.p.	103–104°	103°
a	8.08 ± 0.03 Å	8.10 Å
b	5.85 ± 0.03 Å	5.98
c	35.63 ± 0.12	11.8
β	94° ± 1°	94°
Space group	$P2_1$ or $P2_1/m$	$P2_1/a$
d_{obs}	1.218 g./cm.^{3}	1.06–1.16 g./cm.^{3}

That this hydrocarbon was actually 2-phenylnaphthalene was established on the basis of the following evidence. Values of the molecular weight determined by freezing point depression and the x-ray data were 196 and 211, respectively, which are in substantial agreement with the value 188 ± 10 reported by Lagidze and Petrov. Elemental analysis corresponded to an empirical formula, C_4H_3, and hence to a molecular formula, $C_{16}H_{12}$. Ozonolysis gave a mixture of benzoic and phthalic acids. Finally, direct comparison of the infrared and ul-

traviolet spectra of the hydrocarbon with those of an authentic sample of 2-phenylnaphthalene[2] and a mixture melting point of the two samples established identity.

The result of the earlier crystallographic study is somewhat disturbing as the x-ray method is generally considered to be absolute as far as determining the presence of a center of symmetry in certain space groups. In the present work, then, white specimens of the hydrocarbon showing excellent optical extinction were examined by precession methods in which MoK_α and CuK_α radiations were employed. The symmetry of the crystals was monoclinic. A summary of the results is given in Table I. The only systematic extinctions that were observed are those for *OkO* when *k* is odd. However, reflections of the type *hkl*, with *l* not divisible by three, were very weak or absent and reflections of the type *hOl*, with *h* odd, were extremely weak. Thus the reflections which require a tripling of the *c* axis value given by the previous investigators, and those which violate the space group given by them, are not readily observable unless long exposures are taken and the resulting films are clear.

In addition, the earlier estimate of the crystal density appears to be too low. The present value of 1.218 g./cm.^{3}, the result of several determinations by the flotation method, leads to a molecular weight of 211 if one assumes six molecules in the unit cell, which is in good agreement with the value of 204 g./mole for 2-phenylnaphthalene. The calculated density of the crystal is 1.212 g./cm.^{3}

Finally, our films showed no obvious evidence of disorder in the crystal, such as diffuse reflections or a large temperature factor. These data make it appear highly probable that the compound examined was identical with that previously reported. The present results indicate no restrictions on the molecular symmetry.

Two additional compounds were separated from the lower boiling fraction by distillation. One of these was established as acetophenone by comparison of infrared spectra and 2,4-dinitrophenylhydrazones. A second carbonyl component, b.p. 151–153°/7 mm., was isolated whose physical properties corresponded fairly closely to those reported by Lagidze for the $C_{12}H_{14}O$ ketone which had been tentatively assigned structure (II).

This ketone was identified as 5,6,7,8-tetrahydro-2-acetonaphthone[3] on the basis of the following evidence. An examination of the infrared spectrum suggested the presence of a conjugated methyl ketone, methylene groups, and a trisubstituted benzenoid ring. An iodoform reaction gave an acid, m.p. 151–152.5°, with a neutral equivalent of 178±2. The elemental analysis of this acid was consistent with a molecular formula $C_{11}H_{12}O_2$.[4] Oxidation of the ketone with potassium permanganate gave a tricarboxylic acid, m.p. 210–219° (dec.), with an equivalent weight of 71.5±2. This acid did not depress the melting point of an authentic sample of benzene-1,2,4-tricarboxylic acid but only slightly depressed that of benzene-1,2,3-tricarboxylic acid. Confirmation of the identity was obtained by conversion to the anhydride, m.p. 165–167° and a mixture melting point with an authentic sample.[5]

These data establish this $C_{12}H_{14}O$ ketone as 5,6,7,8-tetrahydro-2-acetonaphthone.

EXPERIMENTAL

Reaction of benzene with 2-butyne-1,4-diol diacetate. To a mixture of 40 g. (0.25 mole) of 2-butyne-1,4-diol diacetate[6] and 420 g. (5.4 moles) of dry benzene was added 78.0 g. (0.59 formula weight) of anhydrous sublimed aluminum chloride over a period of 30 min. After this mixture had been heated at the reflux temperature for 6 hr., it was cooled and then cautiously diluted with 300 ml. of water. The aqueous layer was washed with three 150-ml. portions of benzene. The combined benzene solution was washed with three 100-ml. portions of 1*N* hydrochloric acid and then it was dried over sodium sulfate. After the bulk of the benzene had been removed by distillation, the residue, subjected to a short path distillation, gave 18.7 g. of a liquid fraction, b.p. 43–136°/0.5 mm. and a viscous residue from which 3.0 g. of crystalline hydrocarbon was obtained by sublimation at 150°/0.5 mm. This hydrocarbon, which proved to be 2-phenylnaphthalene, had m.p. 103–104°[2] after resublimation and recrystallization.

Anal. Calcd. for $C_{16}H_{12}$: C, 94.09; H, 5.92; mol. wt. 204. Found: C, 94.37, 94.39; H, 6.00, 6.18; mol. wt. 196 (Rast), 211 (x-ray).

The yield of liquid products was increased by reaction under dilute conditions. To a vigorously stirred mixture of 157 g. (1.19 moles) of aluminum chloride, 92 g. (1.18 moles) benzene, and 300 ml. of petroleum ether C, 50 g. (0.29 mole) of 2-butyne-1,4-diol diacetate was added over a period of 1 hr. at 60°. The mixture was stirred at the reflux temperature for 24 hr. and then worked up as previously described. The products which distilled at 46–203°/7 mm. weighed 80.3 g. The crude product was distilled through a 20-cm. spiral wire column: 1. 93–140°/24 mm., n_D^{25} 1.5333, 23 g.; 2. 120–151°/7 mm., 14 g.; 3. 151–153°/7 mm., n_D^{25} 1.5517, 8.0 g.

Identification of the hydrocarbon as 2-phenylnaphthalene. A sample (501 mg.) of the hydrocarbon (m.p. 103–104°) in 50 ml. of ethyl acetate was treated for 16 min. at 0° with a stream of ozone at a rate of 15.1 mg. of ozone per minute. At the completion of the addition, 30 ml. of glacial acetic acid and 10 ml. of 35% hydrogen peroxide were added and the solution was heated at the reflux temperature for 20 hr. After the solvent had been removed by distillation under reduced pressure, the solid residue was dissolved in 25 ml. of 10% aqueous sodium bicarbonate. The solution was extracted with ether and then acidified with dilute hydrochloric acid. The solution was extracted with two 100-ml. portions of ether, the ether solution was dried over sodium sulfate, and then the solvent was removed by distillation. Sublimation of the residue at 85°/0.1 mm. gave 212 mg. of a

(2) F. D. Chattaway and W. H. Lewis, *J. Chem. Soc.*, 869 (1894).

(3) G. Baddely, E. Wrench, and R. Williams, *J. Chem. Soc.*, 2110 (1953).

(4) J. W. Williams and J. M. Osborn, *J. Am. Chem. Soc.*, 61, 3438 (1939).

(5) The authors wish to thank Dr. L. I. Smith for samples of benzene-1,2,3-tricarboxylic acid and benzene-1,2,4-tricarboxylic acid.

(6) A. W. Johnson, *J. Chem. Soc.*, 1009 (1946).

solid mixture. Resublimation of this material gave benzoic acid m.p. 115–120° which, after recrystallization from water, melted at 120–122° alone or when mixed with an authentic sample, and phthalic anhydride, m.p. 125–132°, the identity of which was also established by a mixture melting point and by comparison of infrared spectra.

Final confirmation of the structure of the hydrocarbon[7] was obtained by comparison of it with 2-phenylnaphthalene.

Identification of fraction 3 as 5,6,7,8-tetrahydro-2-acetonaphthone. Small portions of a solution containing iodine (10 g.) and potassium iodide (20 g.) in water (100 ml.) were added to a mixture of 1.0 g. of fraction 3, (b.p. 151–153°, n_D^{25} 1.5517), described above, 5 ml. of 10% sodium hydroxide, and 20 ml. of dioxane, until a permanent color appeared. The mixture was diluted with water to 150 ml. The iodoform was separated by filtration and the filtrate was treated with two 20-ml. portions of ether. The aqueous solution was acidified to *p*H 2 with concentrated hydrochloric acid. After the excess free iodine had been reduced by the addition of sodium bisulfite, the product was separated from the solution by extraction with three 50-ml. portions of ether. The residue, after removal of the ether by distillation, was dissolved in 50 ml. of 10% aqueous sodium bicarbonate. The crude acid was collected after acidification of the basic solution with hydrochloric acid. Purification of the acid proved to be difficult. However, it was found that after the acid had been sublimed at 125°/0.5 mm., it could be recrystallized from petroleum ether B to give colorless crystals melting at 151–152.5°. 5,6,7,8-Tetrahydro-2-naphthoic acid has been reported to melt at 153°.[4]

Anal. Calcd. for $C_{11}H_{12}O_2$: C, 74.98; H, 6.87; neut. equiv. 176. Found: C, 75.30; H, 6.87; neut. equiv. 178.0, 178.7.

A mixture of 1.0 g. of this ketone, 5 ml. of 10% aqueous sodium hydroxide, 5.0 g. of potassium permanganate, and 75 ml. of water, was heated at the reflux temperature and stirred vigorously for 30 min. An additional 5.0 g. of permanganate was added during the next hour. After an additional 3 hr. of heating and stirring, the solution was acidified and sufficient sodium sulfite was added to reduce the manganese dioxide. The product was extracted with several portions of ether. After the ether had been removed by distillation, the product was recrystallized from a carbon tetrachloride–petroleum ether B mixture to give a colorless acid, m.p. 195–202° (dec.), neut. equiv. 71.7, which did not depress the melting point of benzene-1,2,4-tricarboxylic acid[5] but only depressed the melting point of benzene-1,2,3-tricarboxylic acid by 1°. Positive identification of this acid was attained by conversion to the anhydride by sublimation at 210°/1 mm. The product obtained did not depress the melting point of benzene-1,2,4-tricarboxylic acid anhydride, m.p. 165–167°.

Acetophenone. A sample of fraction 1, on treatment with 2,4-dinitrophenylhydrazine reagent, gave a 2,4-dinitrophenylhydrazone, m.p. 240–245° which did not depress the melting point of an authentic sample of benzophenone-2,4-dinitrophenylhydrazone, m.p. 243–246°.

Treatment of 0.5 g. of fraction 1 with sodium hypoiodite yielded 0.2 g. of an acid, m.p. 120–122°. A mixture of this acid and benzoic acid melted at 120–122°.

MINNEAPOLIS, MINN.

(7) A similar conclusion regarding the structure of this hydrocarbon was obtained by G. Maier, *Ber.*, 90, 2949 (1957).

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

Pyrolysis of Esters. XIII. Pyrolysis of Amides[1,2]

WILLIAM J. BAILEY AND CHARLES N. BIRD[3]

Received November 26, 1957

Amides have been shown to pyrolyze in a manner very similar to that of esters but at a higher temperature. Pyrolysis of *N*-(2-acetoxyethyl)-*N*-ethylacetamide produced cleavage at both the ester and the amide linkages to form *N*-ethylacetamide and vinyl acetate as well as acetic acid and *N*-vinyl-*N*-ethylacetamide. Cleavage of *N*-(1,3-dimethylbutyl)acetamide occurred at 590° to produce acetamide plus impure 4-methyl-1-pentene. Cleavage of the corresponding *N*-methyl dialkylated derivative occurred at 570° to produce *N*-methylacetamide plus a mixture of 4-methyl-1-pentene and 4-methyl-2-pentene. Similarly, cleavage of *N*-(1,3-dimethylbutyl)acetanilide occurred at 510° to produce a 91% yield of acetanilide and a 72% yield of a mixture of the two possible olefins. Pyrolysis of the *tert*-alkylamide, *N*-(1,1,3,3-tetramethylbutyl)-acetamide also occurred at 510° to produce acetamide and a mixture of two olefins.

It was shown in this laboratory that the pyrolysis of esters was an excellent method for the synthesis of strained dienes, such as 1,2-dimethylene-4-cyclohexene,[4] provided that charring was eliminated. Since the pyrolysis usually follows the Hofmann rule in direction of elimination, many interesting monomers and olefins can be prepared by this procedure.[5] Although the pyrolysis of esters has been widely used, very little information is available concerning the pyrolysis of the nitrogen analogs, the amides. Primary amides are known to dehydrate when they are heated to produce good yields of the corresponding nitriles and, under slightly more vigorous conditions, to produce the corresponding imide plus ammonia and the carboxylic acid.[6] None of these reactions is, however,

(1) Previous paper in this series, *J. Org. Chem.*, 22, 1189 (1957).

(2) Presented before the Division of Organic Chemistry at the 132nd National Meeting of the American Chemical Society, New York, N. Y., September 1957.

(3) Office of Naval Research Fellow, 1951–55.

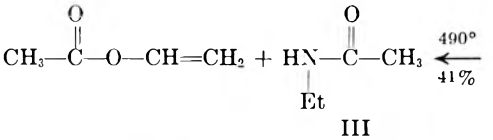
(4) W. J. Bailey and J. Rosenberg, *J. Am. Chem. Soc.*, 77, 73 (1955).

(5) (a) W. J. Bailey and C. King, *J. Am. Chem. Soc.*, 77, 75 (1955); (b) W. J. Bailey, J. J. Hewitt, and C. King, *J. Am. Chem. Soc.*, 77, 357 (1955); (c) W. J. Bailey, J. J. Hewitt, and F. A. Naylor, *J. Org. Chem.*, 22, 1076 (1957).

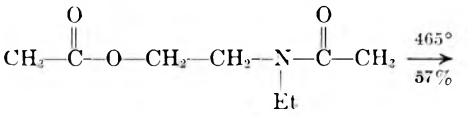
(6) (a) R. S. Boehner and C. E. Andrews, *J. Am. Chem. Soc.*, 38, 2503 (1916); (b) R. S. Boehner and A. L. Ward, *J. Am. Chem. Soc.*, 38, 2505 (1916); (c) D. Davidson and M. Karten, *J. Am. Chem. Soc.*, 78, 1066 (1956).

analogous to the decomposition of an ester to an olefin and an acid. An analogous reaction is possible only with an *N*-alkylamide.

Patents have been issued[7,8] covering the synthesis of *N*-vinylamides by the pyrolysis of acetates of the corresponding amides and cyclic imides. Hexaacetylstreptamine[9] has been pyrolyzed to a mixture of 2,4-diacetimidophenol and 5-acetamido-2-methylbenzoxazole. Burns, Jones, and Ritchie[10] pyrolyzed *N*-acetyl-α-acetoxyisobutyramide to methacrylonitrile and Hagemeyer[11] pyrolyzed α-acetoxypropionamide to acrylonitrile.



III



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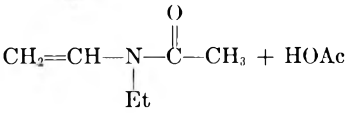

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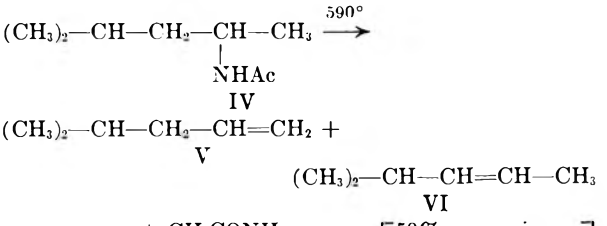
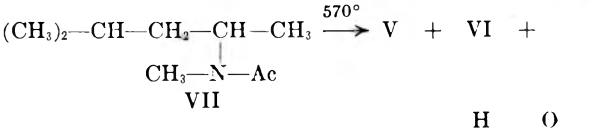
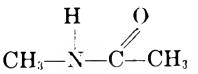
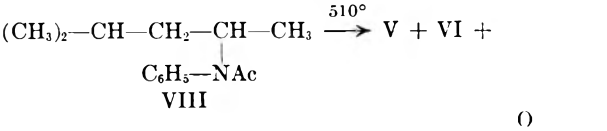
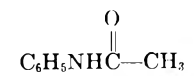


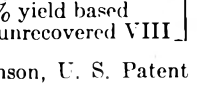
+ CH_3CONH_2 [50% conversion, 68% yield based on unrecovered IV]











[84% conversion, 91% yield based on unrecovered VIII]

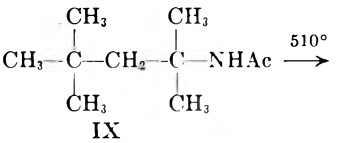
(7) W. E. Hanford and H. B. Stevenson, U. S. Patent **2,231,905** (1941).

(8) W. H. Coover and J. B. Dickey, U. S. Patent **2,585,-230** (1952).

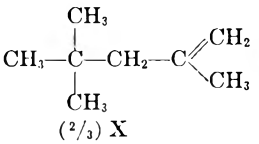
(9) R. L. Peck, C. E. Hoffmine, Jr., E. W. Peel, R. P. Graber, F. W. Holly, R. Mozingo, and K. Folkers, *J. Am. Chem. Soc.*, **68**, 776 (1946).

(10) R. Burns, D. T. Jones, and P. D. Ritchie, *J. Chem. Soc.*, 714 (1935).

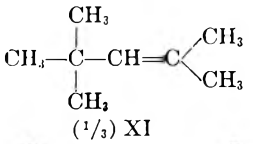
(11) H. Hagemeyer, U. S. Patent **2,417,748** (1947).



IX



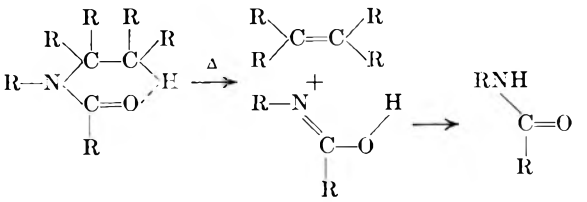
(2/3) X



(1/3) XI

+ CH_3CONH_2 [63% conversion, 92% yield based on unrecovered IX]

For these reasons a series of *N*-substituted amides were prepared and pyrolyzed. The primary purpose of this study was to determine the relative ease of the pyrolysis of an amide compared to an ester under the controlled conditions developed in this laboratory. It was hoped that this information would shed some light on the exact mechanisms of the pyrolyses of amides and esters, which are believed to proceed through a transient six-membered intermediate. Although Hanford and Stevenson[7]



had studied the pyrolysis of *N*-(β-acetoxyethyl)-amides, this problem was reinvestigated under a wider range of conditions. *N*-(2-Acetoxyethyl)-*N*-ethylacetamide (I) was prepared by the acetylation of *N*-ethylethanolamine in a 92% yield. Pyrolysis of this ester-amide I at 465° under conditions that produced very little, if any, charring liberated 63% of the theoretical amount of acetic acid. At the same time a 35% conversion (or 57% yield, based on unrecovered starting material) to *N*-vinyl-*N*-ethylacetamide (II) was realized. The structure of II was indicated by analysis and absorption of 1 mole of hydrogen upon catalytic hydrogenation. In contrast to the *N*-methyl and *N*-phenyl derivatives, II gave a solid polymer of low molecular weight, softening point 122°, when it was treated with boron trifluoride etherate at room temperature; however, the analysis of this polymer was invariably several per cent higher in carbon then expected from pure poly-*N*-vinyl-*N*-ethylacetamide.

In an effort to increase the conversion, the *N*-(2-acetoxyethyl)-*N*-ethylacetamide was pyrolyzed under more vigorous conditions at 490°. A rather surprising result was observed in this experiment. In addition to the expected *N*-vinyl-*N*-ethylacet-

amide (II), a 25% yield of vinyl acetate plus a 41% yield of *N*-ethylacetamide (III) were produced. The *N*-ethylacetamide (III) had the correct analysis and was converted to the known solid hydrochloride. Apparently under these more vigorous conditions the elimination reaction is not as selective, producing a variety of products. It does illustrate that an amide derived from a secondary amine can compete with an ester group (probably by a cyclic six-membered ring) in a thermal decomposition. Several other possible products, such as those resulting from the abstraction of a β-hydrogen on the ethyl group, probably were formed but they were not isolated.

Further study of other *N*-alkylamides was undertaken. Since a series of esters of methylisobutylcarbinol had been studied in order to determine their relative ease of pyrolysis,[12] it appeared that amides related to this series would afford the information necessary to compare the ease of pyrolysis of amides with that of esters.

For this reason *N*-(1,3-dimethylbutyl)acetamide (IV) was prepared from methyl isobutyl ketoxime by catalytic reduction, followed by acetylation. Pyrolysis of IV at 590° produced a 50% conversion to acetamide and a 13% conversion to a mixture of olefins.

Although there was surprisingly little charring at this high temperature, 15% of the material was lost as noncondensable gases during pyrolysis. Since 25% of the starting amide IV was recovered unchanged, the yield of acetamide, based on unrecovered IV, was 67% and the yield of the olefins was only 18%. The infrared absorption spectrum of the mixture of olefins plus refractive index data indicated that the mixture consisted of 4-methyl-1-pentene (V) plus both the *cis*- and *trans*-4-methyl-2-pentene (VI). Thus it appeared that the pyrolysis of an amide of a primary amine requires a temperature more than 100° higher than that of the corresponding ester.

It was of interest to determine the effect of replacing the hydrogen on the nitrogen with an alkyl or an aryl group. The secondary amine, *N*-(1,3-dimethylbutyl)-*N*-methylamine, was prepared in a 91% yield by the reductive alkylation of methylamine with methyl isobutyl ketone in the presence of a copper-chromite catalyst. Acetylation of this amine with acetic anhydride produced the desired *N*-(1,3-dimethylbutyl)-*N*-methylacetamide (VII) in an 87% yield. Pyrolysis of VII at 570° was accompanied by a small amount of charring, and 13% of the material was lost as noncondensable gases. Distillation of the pyrolyzate yielded a 27% conversion to a mixture of olefins and a 44% recovery of crude starting amide VII. Unfortunately, the boiling point of *N*-methylacetamide was so close to that of VII that quantitative recovery of the amides was not accomplished. Infrared measurements as well as refractive index data on the mixture of olefins from the pyrolyzate indicated that the mixture consisted of 4-methyl-1-pentene (V) and 4-methyl-2-pentene (VI) in nearly equal amounts.

An aryl-substituted amide, *N*-(1,3-dimethylbutyl)acetanilide (VIII), was prepared in three steps from methyl isobutyl ketone in an over-all yield of 84%. Azeotropic distillation of the water formed by the reaction of aniline and methyl isobutyl ketone in the presence of zinc chloride gave a 90% yield of *N*-1,3-dimethylbutylideneaniline. Hydrogenation of the anil in the presence of a copper-chromite catalyst gave a 95% yield of the corresponding amine, which was acetylated in a 98% yield to give the desired *N*-(1,3-dimethylbutyl)-acetanilide (VIII). Pyrolysis of the solid VIII at 510° proceeded very smoothly with little or no charring. Distillation of the pyrolyzate gave a 67% conversion to a mixture of olefins and an 84% conversion to acetanilide. Since 8% of the starting amide VIII also was recovered, the yield of the acetanilide, based on unrecovered VIII, was 91% and the yield of the olefin mixture was 72%. Infrared measurements as well as refractive index data indicated that the mixture of olefins consisted of nearly equal amounts of 4-methyl-1-pentene (V) and 4-methyl-2-pentene (VI).

Since it was shown that tertiary esters decompose at a temperature at least 50° below the decomposition temperature of similar secondary esters,[5b] an amide derived from a primary amine attached to a tertiary carbon atom was studied. When *N*-(1,1,3,3-tetramethylbutyl)acetamide (IX) was pyrolyzed at 510°, very little charring occurred. Distillation of the pyrolyzate gave a 41% conversion to a mixture of olefins and a 63% conversion to acetamide. This formation of acetamide appears to be in marked contrast with the work of Ritter and Kalish[13a] who obtained acetonitrile, water, and diisobutylene by the liquid phase pyrolysis of IX. Cook, *et al.*,[13b] also obtained acetonitrile from the treatment of a series of *N*-substituted acetamides with phosphorus pentoxide. Since 32% of the starting amide IX was recovered unchanged, the yield of acetamide, based on unrecovered IX, was 92% and the yield of olefins was 60%. Infrared measurements plus refractive index data indicated that the olefin mixture consisted of approximately two thirds of 2,4,4-trimethyl-1-pentene (X) and one third of 2,4,4-trimethyl-2-pentene (XI).

It is extremely interesting that two of the classes of amides studied, the *N*-*tert*-alkylamide IX and the *N*-alkylanilide VIII, pyrolyzed as conveniently as many esters. The reaction is clean-cut enough in many cases to be of value for the synthesis of

(12) W. J. Bailey and J. J. Hewitt, *J. Org. Chem.*, **21**, 43 (1956).

(13) (a) J. J. Ritter and J. Kalish, *J. Am. Chem. Soc.*, **70**, 4048 (1948); (b) J. W. Cook, G. T. Dickson, D. Ellis, and J. D. Loudon, *J. Chem. Soc.*, 1078 (1949).

olefins. In any event, these pyrolyses should be useful for the degradation of *N*-substituted amines and should compete successfully with the Hofmann exhaustive methylation procedure[14a] or the decomposition of the corresponding amine oxide.[14b] Certainly many of the amides are easier to prepare than the key intermediate in the other two degradative methods.

It can be concluded that amides probably decompose by a cyclic process similar to that proposed for esters although additional work is needed to prove this point.[15] The amides derived from primary amines on this basis would be expected to be more stable than the corresponding esters, since the formation of the enol of an amide requires more energy than the formation of the corresponding carboxylic acid. This effect is partially compensated by the fact that a carbon-nitrogen bond is weaker than a carbon-oxygen bond.[16] The introduction of a substituent on the nitrogen of the amide would be expected to increase the steric strain in the starting amide. Furthermore, any group that would stabilize the enol form might be expected to aid the pyrolysis. Finally, the fact that the *N-tert*-alkylamides decompose at a lower temperature than do the other related amides indicates the similarity between ester and amide pyrolyses.

It should be noted that amides are not as selective in the direction of elimination as originally reported for esters.[5] However, more recent work in this laboratory has shown that the pyrolysis of methylisobutylcarbinyl acetate at 500°, in contrast to earlier work, actually gave a mixture of olefins consisting of 45% 4-methyl-1-pentene (V), 11% *cis*-4-methyl-2-pentene and 44% *trans*-4-methyl-2-pentene (VI). Thus the composition of olefins from the pyrolysis of the amides agrees at least qualitatively with that from the ester pyrolysis.

Although the yields of the amides from all the pyrolyses are in general quite high, the yields of the olefinic products are reasonably high only for the pyrolyses conducted at the lower temperatures. The low yield of the olefins at the high temperatures can be easily rationalized. Recent work, which will be reported separately, has shown that olefins containing a gamma hydrogen are thermally unstable and presumably decompose by a cyclic mechanism. For example, 4-methyl-1-pentene (V) cleaves at 595° to give, as the major product, propylene in a 72% yield. Even more surprising is the fact that 2,4,4-trimethyl-1-pentene (X) will cleave at temperatures as low as 500° into two molecules of isobutylene.

The extension of this study to other amides, including cyclic amides, will be reported separately.

EXPERIMENTAL[17]

N-(2-Acetoxyethyl)-N-ethylacetamide (I). To 775 g. of acetic anhydride heated under reflux was added dropwise 178 g. (2.0 moles) of *N*-ethylethanolamine. After the mixture had been heated under reflux for 12 hr., the excess acetic anhydride and acetic acid were removed under reduced pressure, and the residue was fractionated through a 12-inch Vigreux column to yield 318 g. (92%) of *N*-(2-acetoxyethyl)-*N*-ethylacetamide (I), b.p. 84.2° (0.55 mm.), n_D^{25} 1.4500, d_{25}^4 1.0502.

Anal. Calcd. for $C_8H_{15}O_2N$: C, 55.47; H, 8.73; N, 8.08. Found: C, 55.68; H, 8.44; N, 8.10.

Pyrolysis of N-(2-acetoxyethyl)-N-ethylacetamide (I). *A. Formation of N-vinyl-N-ethylacetamide* (II) *at 465°.* At a rate of 1 g. per minute, 118 g. (0.68 mole) of *N*-(2-acetoxyethyl)-*N*-ethylacetamide (I) was dropped through a vertical Vycor tube packed with glass helices and externally heated at 465° as previously described.[12] A stream of oxygen-free nitrogen was introduced at the top of the tube throughout the pyrolysis. The pyrolyzate was condensed in a 6-inch spiral condenser and collected in a side-inlet flask cooled in a Dry Ice–chloroform bath. The pyrolyzate was distilled through a 12-inch, helix-packed column to produce 60 g. of an azeotrope [11% acetic acid and 89% *N*-vinyl-*N*-ethylacetamide (II)], b.p. 39.6° (3.7 mm.); 83° (40 mm.), a forerun of acetic acid, and 45 g. of recovered starting material. (Titration of aliquot portions of the pyrolyzate indicated that 63% of the theoretical amount of acetic acid had been liberated.) The azeotrope was dissolved in chloroform and this solution was extracted several times with a 25% potassium carbonate solution. The aqueous extracts were reextracted with chloroform and the combined chloroform solutions were dried over anhydrous potassium carbonate. The solvent was removed under reduced pressure, and the residue was fractionated through a 6-inch, helix-packed column to yield 26.5 g. (35%) of *N*-vinyl-*N*-ethylacetamide (II), b.p. 63.2° (14 mm.), n_D^{25} 1.4732. The yield of II, based on unrecovered starting material, was 57%.

Anal. Calcd. for $C_6H_{11}NO$: C, 63.68; H, 9.80; N, 12.38. Found: C, 64.16; H, 9.64; N, 12.64.

Hydrogenation of 0.92 g. (0.0081 mole) of II in the presence of 0.1 g. of platinum oxide catalyst resulted in the absorption of 201 ml. (99%) of hydrogen in 30 min. at 24°. The vinylamide II also rapidly decolorized a solution of bromine in carbon tetrachloride.

B. Formation of vinyl acetate and N-ethylacetamide (III) *at 490°.* By the use of the same procedure described above, 70 g. (0.404 mole) of *N*-(2-acetoxyethyl)-*N*-ethylacetamide (I) was dropped through the pyrolysis tube at 490° over a period of 1 hr. The pyrolyzate was crudely fractionated through an 8-inch Vigreux column to remove all the material boiling below 126° (28 mm.). These fractions were refractionated through the same column to yield 8.7 g. (25%) of impure vinyl acetate, b.p. 75–77°, n_D^{25} 1.3720–1.3729 [reported[18] b.p. 71–72° (728 mm.)]. (Eastman Kodak vinyl acetate had n_D^{25} 1.3915.)

Continued fractionation of the low boiling fraction through the same column produced 14.3 g. (41%) of *N*-

(14) (a) A. W. Hofmann, *Ber.*, **14**, 494, 659 (1881); (b) A. C. Cope, T. T. Foster, and P. H. Towle, *J. Am. Chem. Soc.*, **71**, 3929 (1949).

(15) C. D. Hurd and F. H. Blunck, *J. Am. Chem. Soc.*, **60**, 2419 (1938).

(16) L. Pauling, *Nature of the Chemical Bond*, 2nd ed., Cornell University Press, Ithaca, N. Y., 1948, p. 53.

(17) The authors are grateful to Dr. Mary Aldridge and Miss Kathryn Gerdeman for the analyses and to Dr. E. R. Lippincott and Dr. R. Schroeder for aid in the interpretation of the infrared spectra. The infrared spectra were determined on the pure liquids in a Perkin-Elmer infrared model 12-C spectrometer modified for double-pass operation. All melting points are corrected.

(18) A. Skrabal and A. Zahorka, *Monatsh.*, **48**, 459 (1927).

ethylacetamide (III), b.p. 48° (0.37 mm.), b.p. 206.5–207.5° (763 mm.), n_D^{25} 1.4306 (reported[19] b.p. 206°).

Anal. Calcd. for C_4H_9NO: C, 55.14; H, 10.41. Found: C, 55.41; H, 10.09.

This material did not decolorize a solution of bromine in carbon tetrachloride. Dry hydrogen chloride was bubbled through 4 to 5 drops of the liquid *N*-ethylacetamide (III) to produce a hygroscopic crystalline mass of *N*-ethylacetamide hydrochloride, m.p. 76–77.5° (measured in a stoppered test tube on a bulk sample) (reported[20] m.p. "about" 60°).

Pyrolysis of N-(1,3-dimethylbutyl)acetamide (IV). *N*-1,3-Dimethylbutylamine was prepared by the catalytic hydrogenation of methyl isobutyl ketoxime (Ames Laboratories, Inc., South Norwalk, Conn.) according to the method of Smith and Adkins.[21] Acetylation of the resulting amine with acetic anhydride, followed by fractionation of the reaction mixture through a 17-inch, helix-packed column, produced an 86% yield of *N*-(1,3-dimethylbutyl)acetamide (IV),[22] b.p. 71° (0.4 mm.), n_D^{25} 1.4380 [reported[21] b.p. 94–95° (1 mm.), n_D^{25} 1.4378].

At the rate of 1 g. per minute, 59 g. (0.412 mole) of *N*-(1,3-dimethylbutyl)acetamide (IV) was dropped through a vertical Vycor tube which was heated externally at 590° as described previously. Dry, oxygen-free nitrogen was passed through the tube at a rate of 60 bubbles per minute. The pyrolysis receiver was transferred directly to a distillation column and the material boiling below 75° (16 mm.) was removed quite rapidly to yield 10.82 g. of crude distillate. This material was refractionated through a 6-inch, helix-packed column to yield 4.7 g. of a low-boiling forerun, b.p. 25–46°, and 4.97 g. (14.3%) of a mixture of 4-methyl-1-pentene (V), and 4 methyl-2-pentene (VI), b.p. 46.5–50.0° (730 mm.), n_D^{25} 1.3800–1.3834 (reported[23] for V, b.p. 53.6–53.9°, n_D^{20} 1.3825; reported[24] for the isomeric 4-methyl-2-pentene (VI), b.p. 58.6–59.0°, n_D^{25} 1.3869).

The infrared absorption spectrum of the olefin obtained from the pyrolysis was compared with the spectra reported for 4-methyl-1-pentene (V),[25a] *cis*-4-methyl-2-pentene,[25b] and *trans*-4-methyl-2-pentene[25c] (VI). These data indicated that the olefin mixture was largely 4-methyl-1-pentene (V) but that both *cis*- and *trans*-4-methyl-2-pentene (VI) were present in substantial amounts.

The higher-boiling residues from the two distillations were fractionated through a 6-inch, helix-packed column to yield 15.0 g. (26% recovery) of unchanged *N*-(1,3-dimethylbutyl)acetamide (IV) and 12.1 g. (50%) of impure acetamide, b.p. 96–110°. Two recrystallizations of this acetamide from a 1:10 methanol-ether mixture produced pure material, m.p. 81.2–82.0° (reported[26] m.p. 82–83°). A mixed melting point determination of this sample with an authentic sample of acetamide showed no depression.

At 570° pyrolysis of IV gave a 20% yield of olefin and a 30% yield of acetamide.

N-(1,3-Dimethylbutyl)-N-methylamine. To a hydrogenation vessel which had been cooled to −22° were added 212 g. (2.12 moles) of methyl isobutyl ketone, 306 g. of absolute ethanol, 15.3 g. of copper-chromium oxide catalyst, and 103 ml. (2.5 moles) of anhydrous methylamine. At 180° and 170 atmospheres pressure the theoretical amount of hydrogen was absorbed. The catalyst was removed by filtration and the filtrate was fractionated through an 18-inch, helix-packed column to yield 221 g. (91%) of *N*-(1,3-dimethylbutyl)-*N*-methylamine, b.p. 62–63° (89 mm.), n_D^{25} 1.4080.

Anal. Calcd. for $C_7H_{17}N$: C, 73.04; H, 14.78. Found: C, 73.52; H, 14.46.

N-(1,3-Dimethylbutyl)-N-methylacetamide (VII). To a heated mixture of 215 g. (2.1 moles) of acetic anhydride and 126 g. (2.1 moles) of glacial acetic acid was added dropwise over a period of 1.5 hr., 121.5 g. (1.05 moles) of *N*-(1,3-dimethylbutyl)-*N*-methylamine. After the mixture had been heated at 100–110° for an additional 2 hr., the excess acetic anhydride was hydrolyzed with 35 ml. of water. After the excess acetic acid was removed by distillation under reduced pressure, the residue was dissolved in 750 ml. of ether. This solution was washed successively with three 100-ml. portions of 0.05*N* hydrochloric acid, three 100-ml. portions of a 15% sodium carbonate solution, and two 100-ml. portions of water. After the ether solution had been dried over magnesium sulfate, it was distilled through an 18-inch, helix-packed column to yield 144 g. (87%) of crude amide, b.p. 72.5° (2.4 mm.). Recrystallization from *n*-pentane at −22° produced 136 g. of pure liquid *N*-(1,3-dimethylbutyl)-*N*-methylacetamide (VII), n_D^{25} 1.4430.

Anal. Calcd. for $C_9H_{19}NO$: C, 68.74; H, 12.18, N, 8.91. Found: C, 68.97, H, 11.88, N, 9.16.

Pyrolysis of N-(1,3-dimethylbutyl)-N-methylacetamide (VII). At the rate of 1.2 g. per minute, 52.4 g. (0.33 mole) of *N*-(1,3-dimethylbutyl)-*N*-methylacetamide (VII) was dropped through the standard pyrolysis apparatus at 570°. The pyrolyzate (45.3 g.) was then flash-distilled under reduced pressure to yield 12.8 g. of crude olefin, b.p. 25–75° (100 mm.), n_D^{25} 1.3856. Refractionation of the crude olefin fraction through a 6-inch, helix-packed column produced 7.7 g. (27%) of a mixture of 4-methyl-2-pentene (VI) and 4-methyl-1-pentene (V), b.p. 48–58°, n_D^{25} 1.3853–1.3869. The infrared absorption spectrum indicated that there was slightly more than 50% of the isomeric 4-methyl-2-pentenes (VI) in the mixture.

The higher boiling residue from the pyrolyzate was fractionated through the same column to yield 23.3 g. of a mixture of the starting amide and *N*-methylacetamide, b.p. 63.6–72.2° (2.5 mm.), n_D^{25} 1.4364–1.4434 [reported[27] for *N*-methylacetamide, b.p. 140.5° (90 mm.), n_D^{25} 1.4301). No convenient method of quantitative separation of the *N*-methylacetamide and the starting amide VII was found.

Pyrolysis of *N*-(1,3-dimethylbutyl)-*N*-methylacetamide (VII) at 555° produced a 21% yield of a mixture of olefins, b.p. 46–57°, n_D^{25} 1.3840–1.3858.

N-(1,3-Dimethylbutylidene)aniline. In a 1-l., three-necked flask, fitted with a Dean-Stark trap, a condenser, and a drying tube, were placed 93 g. (1.0 mole) of freshly distilled aniline, 100 g. (1.0 mole) of methyl isobutyl ketone, 300 ml. of dry toluene, and 0.7 g. of pulverized anhydrous zinc chloride. After the mixture had been heated under reflux for 29 hr. and 16.7 ml. (92%) of water had been collected, the zinc chloride was removed by filtration. The solvent was removed by rapid distillation under reduced pressure, and the residue was distilled through an 18-inch, helix-packed column to yield 158 g. (90%) of *N*-(1,3-dimethylbutylidene)-aniline, b.p. 65° (0.9 mm.), n_D^{25} 1.5106 [reported[28] b.p. 107° (11 mm.) and no yield].

Anal. Calcd. for $C_{12}H_{17}N$: C, 82.23; H, 9.78. Found: C, 82.17; H, 9.54.

N-(1,3-Dimethylbutyl)aniline. In a 300-ml. hydrogenation vessel were placed 72 g. (0.41 mole) of *N*-(1,3-dimethylbutylidene) aniline, 72 ml. of absolute alcohol, and 3.6 g. of copper-chromium oxide catalyst and the contents were shaken at

(19) H. O. Nicholas and J. L. E. Erickson, *J. Am. Chem. Soc.*, **48**, 2174 (1926).

(20) A. W. Titherly, *J. Chem. Soc.*, 391 (1901).

(21) M. E. Smith and H. Adkins, *J. Am. Chem. Soc.*, **60**, 657 (1938).

(22) The authors are indebted to Dr. Robert Barclay, Jr., for the preparation of this compound.

(23) C. G. Schmitt and C. E. Boord, *J. Am. Chem. Soc.*, **54**, 754 (1932).

(24) S. P. Mulliken, R. L. Wakeman, and H. T. Gerry, *J. Am. Chem. Soc.*, **57**, 1605 (1935).

(25) (a) American Petroleum Institute Research Project 44, *Infrared Spectral Data*, Carnegie Institute of Technology, Serial No. 710; (b) Serial No. 929; (c) Serial No. 931.

(26) E. C. Wagner, *J. Chem. Educ.*, **7**, 1135 (1930).

(27) C. Naegli, L. Gruntuch, and P. Lendorff, *Helv. Chim. Acta*, **12**, 255 (1929).

(28) I. G. Farbind. A.-G., French Patent **838,434** (1939) [*Chem. Abstr.*, **33**, 7817 (1939)].

150° with hydrogen at 160 atmospheres pressure. After the theoretical amount of hydrogen had been absorbed, the contents of the bomb were filtered and the solvent was removed from the filtrate by distillation under reduced pressure. The residue was fractionated through a 24-inch, helix-packed column to yield 69.2 g. (95%) of *N*-(1,3-dimethylbutyl)-aniline, b.p. 60.5° (0.4 mm.), n_D^{25} 1.5165 (reported[29] in "rather mediocre yields" but with no physical constants).

Anal. Calcd. for $C_{12}H_{19}N$: C, 81.30; H, 10.80. Found: C, 81.29; H, 10.56.

N-(1,3-Dimethylbutyl)acetanilide (VIII). To a mixture of 114 ml. of glacial acetic acid and 188 ml. (2.0 moles) of acetic anhydride heated under reflux in a 1-l., three-necked flask, equipped with a magnetic stirrer, a condenser, and a dropping funnel, was added dropwise over 30 min. 177.3 g. (1.0 mole) of *N*-(1,3-dimethylbutyl)aniline. After the mixture had been heated under reflux for an additional hour, the excess acetic anhydride and acetic acid were removed by distillation under reduced pressure. The residue was dissolved in 500 ml. of ether and the solution was extracted successively with two 50-ml. portions of 0.05*N* hydrochloric acid, three 50-ml. portions of 15% sodium carbonate solution, and two 50-ml. portions of water. After the ether solution had been dried over magnesium sulfate, the ether was removed by distillation. The residue was recrystallized twice from petroleum ether (30–60°) to produce 214.2 g. (98%) of *N*-(1,3-dimethylbutyl)acetanilide (VIII), m.p. 49.1–50.0° (reported[29] m.p. 67° for the acetylated product from the reductive alkylation of aniline with isopropyl alcohol or methylisobutylcarbinol but with no yield or analysis).

Anal. Calcd. for $C_{14}H_{21}NO$: C, 76.66; H, 9.65. Found: C, 76.92; H, 9.85.

Pyrolysis of N-(1,3-dimethylbutyl)acetanilide (VIII). At the rate of 1.2 g. per minute, 54.5 g. (0.25 mole) of molten *N*-(1,3-dimethylbutyl)acetanilide (VIII) was added dropwise from a heated dropping funnel to the pyrolysis tube at 510°. The pyrolyzate (52.7 g.) was collected in a cooled side-inlet flask connected directly to the pyrolysis tube. The low boiling products of the pyrolysis were removed under reduced pressure while the pyrolyzate was maintained at 75°. The crude olefin fraction was refractionated through a 6-inch, helix-packed column to yield 14 g. (67%) of a mixture of 4-methyl-1-pentene (V) and 4-methyl-2-pentene (VI), b.p. 47–58°, n_D^{25} 1.3839–1.3852. The infrared absorption spectrum indicated that this mixture was composed of nearly equal parts of the 4-methyl-1-pentene (V) and 4-methyl-2-pentene (VI).

The solid residue from the pyrolyzate was crushed and extracted for 5.5 hr. with petroleum ether (30–60°) in a Soxhlet extractor. The insoluble material in the cup plus a few crystals in the petroleum ether extract were dried to yield 28.2 g. (84%) of nearly pure acetanilide, m.p. 111–113°. A mixed melting point determination with an authentic sample of acetanilide showed no depression.

The solvent was removed from the petroleum ether solution from the Soxhlet extractor by evaporation, and the residue was recrystallized from petroleum ether to yield 4.1 g. (7.5% recovery) of the starting anilide VIII, m.p. 46–48°. The yield of the olefin mixture, based on unrecovered starting material, was 72% and that of the acetanilide was, therefore, 91%.

N-(1,1,3,3-tetramethylbutyl)acetamide (IX). To a hot mixture of 120 g. (2.0 moles) of glacial acetic acid and 204 g. (2.0 moles) of acetic anhydride was added 129 g. (1.0 mole) of 1,1,3,3-tetramethylbutylamine[30] over a period of 2 hr. After the mixture had been heated at 90–95° for an additional hour, the excess acetic anhydride and acetic acid were removed by distillation under reduced pressure. The residue was suspended in 1.5 l. of ether and the mixture was cooled. The precipitate was removed by filtration and dried in a vacuum desiccator to yield 164 g. (96%) of slightly impure amide. Recrystallization of this material from petroleum ether (60–80°) yielded white needles of pure *N*-(1,1,3,3-tetramethylbutyl)acetamide (IX), m.p. 99.5–100° (reported[31] m.p. 98–99°, with no yield).

Pyrolysis of N-(1,1,3,3-tetramethylbutyl)acetamide (IX). At the rate of 0.8 g. per minute, 56.3 g. (0.33 mole) of molten *N*-(1,1,3,3-tetramethylbutyl)acetamide (IX) was dropped from a heated dropping funnel (130°) through the pyrolysis tube at 510°. The pyrolyzate (55 g.) was condensed in a steam-heated coil condenser and collected in a side-inlet flask cooled in ice. The volatile fraction was removed by distillation under reduced pressure by heating the pyrolyzate at 80°. Fractionation of this low-boiling material through a 6-inch, helix-packed column gave 5.8 g. of a forerun and 13.4 g. (35%) of a mixture of 2,4,4-trimethyl-1-pentene (X) and 2,4,4-trimethyl-2-pentene (XI), b.p. 52–56° (130–140 mm.), n_D^{25} 1.4071–1.4116 [reported[32] for X, b.p. 101° (760 mm.), n_D^{20} 1.4082, and for XI, b.p. 104.5° (760 mm.), n_D^{20} 1.4158]. Comparison of the infrared absorption spectrum of this mixture with those of 2,4,4-trimethyl-1-pentene (X)[33a] and 2,4,4-trimethyl-2-pentene (XI)[33b] indicated that the mixture consisted of about two thirds of the 1-isomer X and one third of the 2-isomer XI.

After the solid residue from the pyrolyzate plus 50 ml. of water were heated for several minutes on the steam bath, the resulting mixture was cooled in ice. The insoluble material was removed by filtration to yield 17.8 g. (32% recovery) of the starting amide, m.p. 99–100°. Water was removed from the filtrate by distillation under reduced pressure to yield 12.2 g. (63%) of impure acetamide, m.p. 71–77°. Two recrystallizations of this crude material from a 1:10 methanol-ether mixture gave nearly pure acetamide, m.p. 80–81°. A mixed melting point determination with an authentic sample of acetamide showed no depression.

The yield of olefins, based on unrecovered starting material, was, therefore, 53%, and the yield of acetamide was 92%.

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(29) A. Guyot and M. Fournier, *Bull. soc. chim.*, [4], **47**, 203 (1930).

(30) The authors are indebted to the Rohm & Haas Co. for a generous supply of this amine.

(31) F. C. Whitmore, C. D. Wilson, J. V. Capinjola, C. O. Tongberg, G. H. Fleming, R. V. McGrew, and J. N. Crosby, *J. Am. Chem. Soc.*, **63**, 2035 (1941).

(32) C. O. Tongberg, J. D. Pickens, M. R. Fenske, and F. C. Whitmore, *J. Am. Chem. Soc.*, **54**, 3706 (1932).

(33) (a) American Petroleum Institute Research Project 44, *Infrared Spectral Data*, Carnegie Institute of Technology, Pittsburgh, Pa., Serial No. 725; (b) Serial No. 825.

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

Pyrolysis of Esters. XIV. Synthesis of 1,3-Dimethylenecyclohexane[1]

WILLIAM J. BAILEY AND JAMES ECONOMY[2]

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The pyrolysis of hexahydroisophthalyl diacetate at 555° gave a 94% yield of 1,3-dimethylenecyclohexane. This ester was studied since the product possesses the tendency to rearrange to form a conjugated system as well as the driving force of an exocyclic double bond to form an endocyclic double bond. The fact that little or no rearrangement to the conjugated diene occurred indicates that the pyrolysis of esters is a very mild method for the introduction of unsaturation.

The pyrolysis of esters has been shown to be an excellent method for the synthesis of olefins free from isomeric impurities formed by rearrangement.[3,4] This pyrolytic method has been particularly useful for the synthesis of cyclic dienes containing strained double bonds in a series of 1,2-dimethylenecyclohexanes.[5-8]

Even though these exocyclic double bonds are strained, there appears to be little or no tendency for rearrangement under pyrolytic conditions, provided that all carbonization is eliminated.

In order to investigate other highly strained dienes that could be synthesized by pyrolysis, a series[9-11] of isomers of aromatic compounds were prepared. For example 1,2-dimethylene-4-cyclohexene,[9] isomeric with *o*-xylene, was prepared in a 92% yield by the pyrolysis of a diacetate. It is noteworthy that the Hofmann decomposition of the corresponding bis quaternary ammonium hydroxide gave only *o*-xylene and none of the exocyclic triene.[12] Similarly, the pyrolysis of a diacetate produced an isomer of *p*-xylene, 1,4-dimethylene-2-cyclohexene.[11] Although the driving force for aromatization is strong in each case, rearrangement of both exocyclic double bonds is required. In the former case the aromatization must be initiated by the rearrangement of one of the exocyclic double bonds into conjugation with the internal double bond.

The pyrolysis of esters has been applied to the synthesis of 1,4-dienes with a variety of successes, depending on the conditions. Schniepp and Geller[13] successfully prepared 1,4-pentadiene by the pyrolysis of 1,5-diacetoxypentane. Similarly, Riobé[14] prepared a series of substituted 1,4-pentadienes by pyrolysis of the corresponding unsaturated acetates. Although Paul and Tchelitcheff have used pyrolysis to prepare 1,4-pentadienes,[15] they also have reported several pyrolyses that should have produced only unconjugated dienes but that have given substantial amounts of the conjugated diene.[15,16] In order to evaluate the mildness of this pyrolytic method still further, it seemed of interest to study an ester that combined the driving force for rearrangement of both these systems, that is, to prepare a cyclic diene that would have as the driving force for rearrangement not only the tendency of the unstable double bond exocyclic to a six-membered ring to shift to an internal position but also the tendency of the double bonds to shift into conjugation. Such a diene was 1,3-dimethylenecyclohexane (I). The pyrolysis of the hexahydroisophthalyl diacetate (IV) to produce the diene I was of further interest since it would give a comparison of the ease of pyrolysis of a diacetate to produce an unconjugated diene with that of the previously studied diacetates that produced conjugated dienes.

The preparation of diethyl isophthalate (II) in an over-all yield of 72% was accomplished by the oxidation of *m*-xylene with potassium permanganate to produce isophthalic acid, which was directly esterified with ethanol by the azeotropic method with benzene. The ester II was reduced with Raney nickel under high pressure to produce a mixture of diethyl *cis*- and *trans*-hexahydroisophthalate (III) in a 96% yield. Treatment of III with lithium aluminum hydride, followed by careful acidification of

(1) Previous paper in this series, *J. Org Chem.*, **23**, 996 (1958).

(2) Office of Naval Research Fellow, 1953-54.

(3) W. J. Bailey, J. J. Hewitt, and C. King, *J. Am. Chem. Soc.*, **77**, 357 (1955).

(4) W. J. Bailey, F. E. Naylor, and J. J. Hewitt, *J. Org. Chem.*, **22**, 1076 (1957).

(5) W. J. Bailey and H. R. Golder, *J. Am. Chem. Soc.*, **75**, 4780 (1953).

(6) W. J. Bailey, J. Rosenberg, and L. J. Young, *J. Am. Chem. Soc.*, **76**, 2251 (1954).

(7) W. J. Bailey, C.-W. Liao, and G. H. Coleman, *J. Am. Chem. Soc.*, **77**, 990 (1955).

(8) W. J. Bailey and W. A. Klein, *J. Am. Chem. Soc.*, **79**, 3124 (1957).

(9) W. J. Bailey and J. Rosenberg, *J. Am. Chem. Soc.*, **77**, 73 (1955).

(10) W. J. Bailey, J. Rosenberg, and L. J. Young, *J. Am. Chem. Soc.*, **77**, 1163 (1955).

(11) W. J. Bailey and R. Barclay, Jr., Abstracts of the 130th National Meeting of the American Chemical Society, Atlantic City, N. J., September 1956.

(12) J. E. Ladbury and E. E. Turner, *J. Chem. Soc.*, 3885 (1954).

(13) L. E. Schniepp and H. E. Geller, *J. Am. Chem. Soc.*, **67**, 54 (1945).

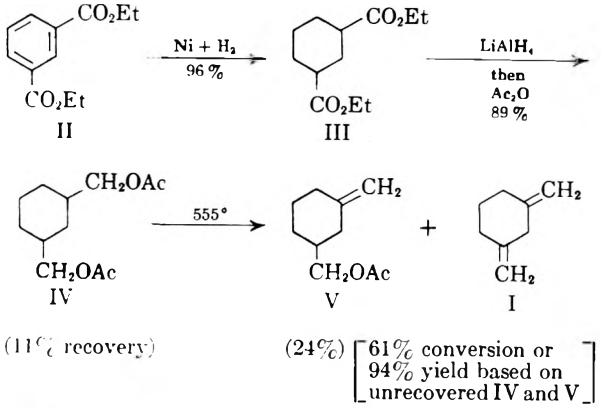
(14) O. Riobé, *Compt. rend.*, **226**, 1625 (1948).

(15) R. Paul and S. Tchelitcheff, *Bull. soc. chim. France*, **15**, 108 (1948).

(16) R. Paul and S. Tchelitcheff, *Compt. rend.*, **223**, 1136 (1946).

the complex, produced a 94% yield of a mixture of *cis*- and *trans*-hexahydroisophthalyl alcohol.

An alternative synthesis of the hexahydroisophthalyl alcohol proceeded in a similar fashion from dimethyl isophthalate. Esterification of this alcohol with acetic anhydride produced a mixture of *cis*- and *trans*-hexahydroisophthalyl diacetate (IV) in a 95% yield.



When the diacetate IV was dropped through a pyrolysis tube packed with glass helices at 555° under such conditions that 75% of two molar equivalents of acetic acid was eliminated, a 61% conversion to 1,3-dimethylenecyclohexane (I) and a 24% yield of 3-methylenehexahydrobenzyl acetate were realized. Since 11% of the starting material IV was recovered unchanged, the yield of the diene I, based on unrecovered IV and V, was 94%. At 515° only 30% of two molar equivalents of acetic acid was eliminated. Under comparable conditions (520°), hexahydrophthalyl diacetate liberated 65% of two molar equivalents of acetic acid.[5] Thus it appears that the production of a conjugated diene appreciably aids the elimination of acetic acid.

The structure of the 1,3-dimethylenecyclohexane (I) was indicated by analysis and ultraviolet and infrared absorption spectra. The absence of conjugated double bonds was indicated by the fact that the ultraviolet absorption spectrum showed no maximum or minimum above 220 mμ and the ε was only 25 at 220 mμ. (1,2-Dimethylenecyclohexane[5] has an ε maximum of 10,050 at 220 mμ). Similarly, the most likely rearranged product with one double bond exocyclic and the other endocyclic would be expected to have a maximum absorption above 235 mμ.[17]

The infrared absorption spectrum with strong bands at 3065, 2970, 1770, 1642, 1428–1443, 1350, 1250, 1172, 1070, 1042, 998, 970, 900, 940–960, 770, 732 and 676 cm.$^{-1}$ and weaker bands at 1551, 1395, 1335, 1310, 1272, 1178, 1162, 1102, 988, and and 980 cm.$^{-1}$ is consistent with the presence of two unconjugated methylene groups.

It must be concluded that the tendency for rearrangement during the pyrolysis of esters is indeed quite small. This information should make possible the syntheses of other interesting dienes and the preparation of a new series of isomers of aromatic compounds.

EXPERIMENTAL[18]

Diethyl isophthalate (II). A mixture of 106 g. (1.0 mole) of *m*-xylene, 26 g. of sodium hydroxide, 200 g. of potassium permanganate, and 5 l. of water was heated under reflux for 24 hr. until all of the permanganate color had been discharged. At that time an additional 200 g. of potassium permanganate and 26 g. of sodium hydroxide were added and the heating of the mixture was continued. This process was repeated until a total of 1200 g. of permanganate had been added. The excess potassium permanganate was decomposed with ethanol and the manganese dioxide was removed by filtration. The filtrate was acidified with concentrated hydrochloric acid and the precipitate was removed by filtration. This crude isophthalic acid was not purified but was placed in a 5-l., three-necked flask, equipped with two Dean-Stark traps, together with 1 l. of absolute alcohol, 5 l. of benzene, and 5 ml. of concentrated sulfuric acid. After the mixture had been heated under reflux for 8 days and no additional aqueous phase was formed, the solution was concentrated to about 800 ml. by distillation. The concentrate was extracted with water and then with a saturated sodium bicarbonate solution and dried over magnesium sulfate. After the solvents had been removed by distillation under reduced pressure, the residue was fractionated through a 12-inch, helix-packed column to yield 158 g. (72%) of diethyl isophthalate (II), b.p. 150° (0.7 mm.), n_D^{25} 1.5053 [reported[19] b.p. 170–170.5° (24 mm.), $n_D^{17.5}$ 1.50815].

Diethyl hexahydroisophthalate (III). In a 300-ml. hydrogenation vessel, 111 g. (0.50 mole) of diethyl isophthalate (II) was hydrogenated at 80° and 250 atmospheres pressure in the presence of 8 g. of W-2 Raney nickel catalyst.[20] The amount of hydrogen consumed was 103% of the theoretical amount. After the catalyst had been removed by filtration, the filtrate was fractionated through a 10-inch, Vigreux column to yield 108 g. (96%) of a mixture of diethyl *cis*- and *trans*-hexahydroisophthalate (III), b.p. 127–131° (3.5 mm.), n_D^{25} 1.4494 [reported[21] b.p. 141–151° (15 mm.), n_D^{20} 1.4511].

Dimethyl hexahydroisophthalate. In a high pressure hydrogenation vessel, 487 g. (2.51 moles) of dimethyl isophthalate was hydrogenated at 150° and 307 atmospheres pressure in the presence of 50 g. of W-2 Raney nickel catalyst. After the catalyst had been removed by filtration, the filtrate was distilled through a modified Claisen head to yield 494 g. (98%) of a mixture of dimethyl *cis*- and *trans*-hexahydroisophthalate, b.p. 120° (1.5 mm.), n_D^{25} 1.4545 [reported[21] b.p. 139–148° (20 mm.), n_D^{20} 1.4570].

Hexahydroisophthalyl alcohol. A. From diethyl hexahydroisophthalate (II). To a slurry of 27 g. (0.71 mole) of lithium aluminum hydride in 1000 ml. of ether contained in a 3-l., three-necked flask, equipped with a stirrer, a condenser, and a dropping funnel, was added dropwise 99 g. (0.45 mole) of

(17) W. J. Bailey and J. C. Goossens, *J. Am. Chem. Soc.*, **78**, 2804 (1956).

(18) The authors are indebted to Dr. Mary Aldrich and Kathryn Gerdeman for the microanalyses and to Kathryn Gerdeman and Dr. Robert A. Spurr for the infrared spectrum. The infrared absorption spectrum was determined on the pure liquid with a Perkin-Elmer model 12-C spectrometer modified for double-pass operation. The ultraviolet spectrum was determined in a purified cyclohexane solution with a Beckmann DU spectrophotometer.

(19) K. v. Auwers and M. Schmidt, *Ber.*, **46**, 484 (1913).

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

(21) A. Skita and R. Rossier, *Ber.*, **72**, 265 (1939).

a mixture of diethyl *cis*- and *trans*-hexahydroisophthalate (II) dissolved in 600 ml. of dry ether. After the mixture had been heated under reflux for 48 hr., the excess hydride was decomposed by the addition of 50 ml. of water. The complex was dissolved by the addition of 500 ml. of 10% hydrochloric acid to form a cloudy solution. The aqueous layer was extracted with ether for 11 days in an exhaustive ether extractor. The combined extracts and original ether layer were dried over magnesium sulfate. After the ether had been removed by distillation under reduced pressure, the residue was fractionated through a 10-inch Vigreux column to yield 58.6 g. (94%) of a mixture of *cis*- and *trans*-hexahydroisophthalyl alcohol, b.p. 139° (0.8 mm.), n_D^{25} 1.4879. [Since this work was completed, the preparations of the pure *cis*-hexahydroisophthalyl alcohol, m.p. 55°, and the pure *trans*-hexahydroisophthalyl alcohol, b.p. 112–114° (0.1 mm.), n_D^{24} 1.4941, have been reported[22] starting from the corresponding pure acid in each case.]

Anal. Calcd. for $C_8H_{16}O_2$: C, 66.67; H, 11.11. Found: C, 66.54; H, 10.90

B. From dimethyl hexahydroisophthalate. To a slurry of 105 g. (2.76 moles) of lithium aluminum hydride in 2500 ml. of ether was added dropwise 400 g. (2.0 moles) of a mixture of dimethyl *cis*- and *trans*-hexahydroisophthalate dissolved in 1000 ml. of dry ether. After the reaction mixture had been heated under reflux for 18 hr., the excess hydride was decomposed with 60 ml. of glacial acetic acid and the complex was dissolved with a minimum amount of 10% hydrochloric acid. The aqueous layer was extracted with ether in an exhaustive ether extractor for 6 days. After the combined extracts and original organic layer had been dried over magnesium sulfate, the ether was removed by distillation and the residue was fractionated through a 10-inch Vigreux column to yield 215 g. (75%) of a mixture of *cis*- and *trans*-hexahydroisophthalyl alcohol, b.p. 137–139° (0.8 mm.), n_D^{25} 1.4877.

Hexahydroisophthalyl diacetate (IV). After a mixture of 30 g. (0.21 mole) of a mixture of *cis*- and *trans*-hexahydroisophthalyl alcohol and 1500 ml. of acetic anhydride had been heated under reflux for 48 hr., the excess acetic anhydride and acetic acid were removed by distillation under reduced pressure. The residue was diluted with 100 ml. of ether and the resulting solution was extracted consecutively with water, a saturated solution of sodium carbonate, and a saturated solution of sodium chloride. After the solution had been dried over potassium carbonate, the ether was removed by distillation, and the residue was fractionated through a 10-inch Vigreux column to yield 44 g. (95%) of a mixture of *cis*- and *trans*-hexahydroisophthalyl diacetate (IV), b.p. 94° (0.3 mm.), n_D^{25} 1.4634. [The pure *cis*-hexahydroisophthalyl diacetate, b.p. 105–107° (0.5 mm.), n_D^{15} 1.4598, was recently prepared by a series of involved reactions proceeding through a bicyclic ether.[22]]

Pyrolysis of hexahydroisophthalyl diacetate (IV). At the rate of 36 drops per minute, 166 g. (0.55 mole) of hexahydroisophthalyl diacetate (IV) was added dropwise to a vertical Vycor combustion tube packed with 1/16-inch Pyrex helices and heated externally at 555° as described previously.[23] The apparatus was continuously flushed with a slow stream of oxygen-free nitrogen in order to prevent charring. The pyrolyzate, which was collected in a side-inlet flask cooled in a Dry Ice–acetone bath, was extracted with four 100-ml. portions of water. (Titration of an aliquot of the aqueous extracts indicated that 75% of two molar equivalents of acetic acid had been liberated.) After the organic layer had been dried over potassium carbonate, it was fractionated through a 6-inch, helix-packed column to yield 35.8 g. (61%) of 1,3-dimethylenecyclohexane (I), b.p. 122°, n_D^{25} 1.4697; 22 g. (24%) of 1-methylene-2-acetoxymethylcyclohexane (V), b.p. 62° (2.1 mm.), n_D^{25} 1.4600; and 13.9 g. (11% recovery) of unchanged starting ester IV. The yield of the diene I, based on unrecovered IV and V, was 94%.

Anal. Calcd. for C_8H_{12}: C, 88.89; H, 11.11. Found: C, 89.10; H, 11.06.

Calcd. for $C_{10}H_{16}O_2$: C, 71.43; H, 9.52. Found: C, 71.45; H, 9.38.

A sample of the diene I immediately decolorized a solution of bromine in carbon tetrachloride and a dilute potassium permanganate solution. Failure to obtain a precipitate from the attempted reaction with the diene I and maleic anhydride would indicate the absence of any product formed by the rearrangement of both double bonds into conjugation within the ring.

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(22) G. A. Haggis and L. N. Owen, *J. Chem. Soc.*, 399 (1953).

(23) W. J. Bailey and J. J. Hewitt, *J. Org. Chem.*, 21, 543 (1956).

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

Acid-Catalyzed Condensation of Phenols and Keto Acids

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Phenol, *o*-cresol, and 2,6-xylenol were condensed with various keto acids or their methyl esters, in the presence of acid catalysts, to form *gem*-bis(*p*-hydroxyphenyl) substituted carboxylic acids.

Extensive investigation of phenol has shown that it acts as a non-specific bactericide and fungicide by denaturing the proteins of the microorganisms. The phenols are often used in conjunction with a wetting agent in order that they may permeate freely, spread evenly, and gain ready access to the infected area. We have undertaken a program to incorporate phenolic groups into aliphatic acids of varying chain length with the hope that germicidal and fungicidal activity may be combined with surface-activating properties.

Phenol, *o*-cresol, and 2,6-xylenol have been condensed with a number of keto acids or their methyl esters to form di-*p*-hydroxyphenyl substituted carboxylic acids.

Concentrated sulfuric acid, 70 per cent sulfuric acid, and hydrogen chloride–acetic acid were the

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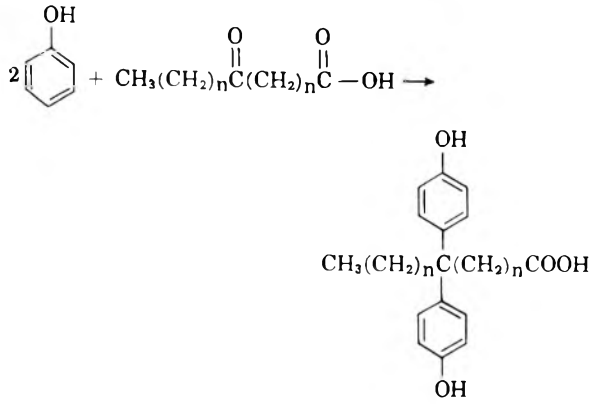

acid catalysts used for these condensations. The selection of the catalyst depends largely on its compatibility with the mixture of phenol and keto acid. Other factors were involved occasionally. For example, hydrogen chloride in acetic acid, phenol, and ethyl acetoacetate gave 3,3-bis(*p*-hydroxyphenyl)butanoic acid instead of undergoing a von Pechmann reaction to form a coumarin.[2] In some cases it was noted that sulfuric acid caused the formation of more polymeric material than did hydrogen chloride-acetic acid.

That the condensation occurred at the *p*-position rather than the *o*-position to the hydroxyl group was indicated by the infrared spectra which had a band at 12.0 μ and no band at 13.2 μ. The condensations were sensitive to steric hindrance. When the carbonyl group of the keto acid was flanked on both sides by relatively long chains, as in methyl 4-ketodecanoate and methyl 6-ketodecanoate, no condensation products were obtained.

The phenol moiety of the condensation products was readily nitrated with nitric acid in glacial acetic acid. Only the *o*-cresol–keto ester condensation products were nitrated in the present investigation. One compound, ethyl 3,3-bis(*p*-hydroxyphenyl)pentanoate, was chlorinated with sulfuryl chloride to form ethyl 3,3-bis(3-chloro-4-hydroxyphenyl)pentanoate.

The keto esters prepared in the course of this work were synthesized by the methods reported by Cason[2a] and Cason and Prout.[2b]

EXPERIMENTAL

Preparation of the methyl esters of keto acids. These compounds were made by previously described procedures.[2] Listed in Table I are the keto acids prepared in this work and their physical constants.

3,3-Bis(p-hydroxyphenyl)butanoic acid (I). Phenol (47 g. 0.05 mole) was dissolved in a mixture of 50 ml. of glacial acetic acid and 13 g. (0.1 mole) of ethyl acetoacetate. Anhydrous hydrogen chloride was passed through the solution for 4 hr. and it was allowed to stand for 7 days. The solution was poured into 400 ml. of water. The precipitated oil was washed twice with water and steam distilled to remove phenol. Sodium hydroxide pellets were dissolved in the solution to make it a 10% sodium hydroxide solution. It was heated to saponify the ester and then acidified. The product separated as an oil. The latter was dissolved in benzene, heated with decolorizing carbon, and dried over magnesium sulfate. The product was obtained as colorless crystals by partial removal of the solvent. It was recrystallized from benzene; yield 56%, m.p. 150°. All attempts to obtain a solvent-free sample failed.

Anal. Calcd. for $C_{16}H_{16}O_4 \cdot 2C_6H_6$: C, 78.48; H, 6.58. Found: C, 78.37; H, 6.73.

The ethyl ester was prepared by heating the acid with excess ethanol in the presence of a small amount of concentrated sulfuric acid. The crude product was obtained by removing the excess ethanol. It was recrystallized from benzene. The yield was 80%, m.p. 127°.

Anal. Calcd. for $C_{18}H_{20}O_4 \cdot 2C_6H_6$: C, 78.91; H, 7.06. Found: C, 78.72; H, 6.99.

3,3-bis(3-Methyl-4-hydroxyphenyl)butanoic acid (II). This compound was prepared from 13 g. (0.1 mole) of ethyl acetoacetate and 43 g. (0.4 mole) of *o*-cresol by the method used for making I. The yield was 49%, m.p. 123° dec.

Anal. Calcd for $C_{18}H_{20}O_4 \cdot 2C_6H_6$: C, 76.16; H, 6.92. Found: C, 75.96; H, 7.04.

3,3-bis(3,5-Dimethyl-4-hydroxyphenyl)butanoic acid (III) was prepared from ethyl acetoacetate and 2,6-xylenol by the same procedure that was used for making II. It was recrystallized from ethanol-water. The yield was 34%, m.p. 196°.

Anal. Calcd. for $C_{20}H_{24}O_4$: C, 73.14; H, 7.37. Found: C, 72.92; H, 7.37. The ethyl ester was obtained by direct esterification using sulfuric acid as the catalyst. The yield was 82%, m.p. 149–150°.

Anal. Calcd. for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 74.27; H, 7.86.

3,3-bis-(3-Methyl-4-hydroxyphenyl)pentanoic acid (IV). A mixture of 260 g. (2.5 mole) of *o*-cresol, and 116 g. (1 mole) of levulinic acid was cooled to 0°. To this mixture, 96 g. of concentrated sulfuric acid was added dropwise with stirring. After standing for 3 days, the viscous, red oil was washed with water and dissolved in 500 ml. of ethyl acetate. The ethyl acetate solution was thoroughly extracted with saturated sodium carbonate solution. Acidification of the carbonate extract gave a heavy oil which was dissolved in benzene, decolorized with Darco, and dried over sodium sulfate. A colorless product was obtained by partially removing the solvent. It was recrystallized from benzene. The yield was 37%, m.p. 96° dec.

Anal. Calcd. for $C_{19}H_{22}O_4 \cdot 2C_6H_6$: C, 74.59; H, 7.19. Found: C, 74.76; H, 7.13.

The *ethyl ester*, prepared as described under I, was obtained as an oil. The latter was dissolved in benzene, decolorized with Darco, and precipitated with petroleum ether. It was recrystallized from methanol-water, yield 50%, m.p. 144°.

Anal. Calcd. for $C_{21}H_{26}O_4$: C, 73.66; H, 7.65. Found: C, 73.62; H, 7.65

TABLE I

PHYSICAL CONSTANTS OF KETO ESTERS

Compound	Yield, %	B.P.	n_D^{25}
Methyl 4-ketohexanoate	71	63°/3 m.m.	1.4258
Methyl 6-ketoheptanoate	77	83–85°/3.5 m.m.	1.4320
Methyl 4-ketooctanoate	71	72°/0.5 m.m.	1.4288
Methyl 6-ketooctanoate	86	76–77°/0.5 m.m.	1.4316
Methyl 4-ketodecanoate	55	104–105°/1.2 m.m.	1.4350

(2) von Pechmann and Duisberg, *Ber.*, 16, 2119 (1883).

2(a) Cason, *Org. Syntheses.*, Coll. Vol. III, 169 (1955); (b) Cason and Prout, *Org. Syntheses*, Coll. Vol. III, 601 (1955).

TABLE II

NITRO DERIVATIVES

Compound	Yield, %	M.P.	Analysis Calcd. C	H	N	Found C	H	N
3,3-*Bis*(3-Me-4-OH-5-NO_2-phenyl)butanoic acid	76	230	55.38	4.64	7.17	55.51	4.61	7.43
4,4-*Bis*(3-Me-4-OH-5-NO_2-phenyl)pentanoic acid	81	234	56.43	4.99	6.93	56.29	5.16	6.80
4,4-*Bis*(3-Me-4-OH-5-NO_2-phenyl)hexanoic acid	71	224	57.41	5.30	6.70	57.43	5.25	6.44
6,6-*Bis*(3-Me-4-OH-5-NO_2-phenyl)heptanoic acid	67	204	58.32	5.60	6.48	58.35	5.65	6.31
6,6-*Bis*(3-Me-4-OH-5-NO_2-phenyl)octanoic acid	70	194	59.18	5.87	6.27	59.01	6.01	6.13

4,4-Bis(3,5-dimethyl-4-hydroxyphenyl)pentanoic acid (V). Levulinic acid (11.6 g., 0.1 mole) was dissolved in a mixture of 75 ml. of glacial acetic acid and 25 g. (0.2 mole) of 2,6-xylenol. Dry hydrogen chloride was passed into the solution for 4 hrs. and it was then allowed to stand for 10 days. The solution was poured into 500 ml. of water and the red oil removed and dissolved in ethyl acetate. The ethyl acetate solution was extracted with saturated sodium carbonate solution. Acidification of the carbonate solution precipitated an oil which solidified on standing. It was recrystallized from ethanol-water, yield 25%, m.p. 198°.

Anal. Calcd. for $C_{21}H_{26}O$: C, 73.66; H, 7.65. Found: C, 73.46; H, 7.74.

4,4-Bis-(p-hydroxyphenyl)hexanoic acid (VI). Phenol (47 g., 0.5 mole) was added to 14.5 g. (0.1 mole) of methyl 4-ketohexanoate. After warming to effect solution, it was cooled to 0° and 10 g. of concentrated sulfuric acid was added dropwise with stirring. After standing for 14 days the mixture was poured into water and the oil treated as in the preparation of I. It was finally recrystallized from toluene; yield 33%, m.p. 183–184°.

Anal. Calcd. for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 71.95; H, 6.52.

4,4-Bis(3-methyl-4-hydroxyphenyl)hexanoic acid (VII). A mixture of 14 g. (0.1 mole) of methyl 4-ketohexanoate and 43 g. (0.4 mole) of *o*-cresol was cooled to 0° and 10 g. of concentrated sulfuric acid added dropwise with stirring. After standing for 7 days the red, viscous oil was worked up by the procedure used for I. The oily product which was obtained when the solution of the sodium salt was acidified was kept at 1–2 mm. at room temperature until it had solidified. The solid was washed with petroleum ether and recrystallized from benzene; yield 61%, m.p. 106° dec.

Anal. Calcd. for $C_{20}H_{24}O_4 \cdot {}^1/_2C_6H_6$: C, 75.17; H, 7.40. Found: C, 75.27; H, 7.60.

The formula showing $^1/_2$ mole of benzene is not to be regarded as established just because it fits the analytical data. The fact that a number of compounds in this investigation had an attraction for benzene is of interest and a study of this behavior will be reported later.

6,6-Bis(3-methyl-4-hydroxyphenyl)heptanoic acid (VIII) was prepared from methyl 6-ketoheptanoate and *o*-cresol by the procedure used for making compound VI. It was recrystallized from benzene. The yield was 44%, m.p. 151–152°.

Anal. Calcd. for $C_{21}H_{26}O_4$: C, 73.66; H, 7.65. Found: C, 73.43; H, 7.67.

6,6-Bis(3,5-dimethyl-4-hydroxyphenyl)heptanoic acid (IX) was prepared from methyl 6-ketoheptanoate and 2,6-xylenol by the method used for making compound I. It was recrystallized from benzene. The yield was 73%, m.p. 177°.

Anal. Calcd. for $C_{23}H_{30}O_4$: C, 74.55; H, 8.16. Found: C, 74.59; H, 8.20.

4,4-Bis(p-hydroxylphenyl)octanoic acid (X) was prepared from methyl 4-ketooctanoate and phenol by the method used for VI. It was recrystallized from xylene; yield 48%, m.p. 139–140°.

Anal. Calcd. for $C_{20}H_{24}O_4$: C, 73.14; H, 7.37. Found: C, 73.04; H, 7.36.

4,4-Bis(3-methyl-4-hydroxyphenyl)hexanoic acid and 6,6-bis(3-methyl-4-hydroxyphenyl)octanoic acid. These compounds were prepared by the procedure used for the condensation of *o*-cresol and the other keto esters. The products were obtained as gummy solids. All attempts to purify them failed. They were successfully nitrated, however, to the 5-nitro compounds.

Preparation of nitro derivatives. In this work only the condensation products from *o*-cresol and keto acids were nitrated. The nitro derivatives are listed in Table II. The general procedure was to suspend about 0.02 mole of the acid in 30 ml. of glacial acetic acid. To this suspension with stirring and cooling, a solution of 6.3 g. (0.1 mole) of nitric acid in 20 ml. of glacial acetic acid was added dropwise. After an induction period of about 1 min., the solution turned red, and fine yellow crystals began to separate. After 1 hr., the crystals were collected, washed with water, and recrystallized from an ethanol-water mixture.

Preparation of ethyl 4,4-bis(3-chloro-4-hydroxyphenyl)-pentanoate. Eight grams (0.025 mole) of ethyl 4,4-bis(*p*-hydroxyphenyl)pentanoate was dissolved in 300 ml. of chloroform and 40 g. (0.3 mole) of freshly distilled sulfuryl chloride added. The solution was refluxed for 3 hr. and the excess sulfuryl chloride and chloroform were removed under reduced pressure. The oily residue was dissolved in benzene and decolorized with Darco. The filtrate was reduced to a small volume under reduced pressure and petroleum ether added until the solution almost remained turbid. After cooling overnight, the product was removed and recrystallized from methanol; yield 41%, m.p. 131°.

Anal. Calcd. for $C_{19}H_{20}O_4Cl_2$: C, 59.54; H, 5.26; Cl, 18.50. Found: C, 59.62; H, 5.41; Cl, 18.51.

PHILADELPHIA, PA.

[CONTRIBUTION FROM MELLON INSTITUTE]

Preparation of Vinyltetramethylbenzenes

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Directions for the preparation of three vinyltetramethylbenzenes are reported.

Three vinyltetramethylbenzenes were prepared for evaluation as monomers—vinyldurene (IV), divinyldurene (VIII), and vinylprehnitene (XI). The general preparative method involved acetylation of the hydrocarbon, hydrogenation of the ketone, and dehydration of the carbinol.

The best procedure for the acetylation of durene to acetodurene was a modification of the Perrier method[1] in which durene was added to the preformed aluminum chloride–acetyl chloride complex in carbon tetrachloride. Diacetoisodurene was coproduct when acetic anhydride was added to a mixture of durene and a large excess of aluminum chloride in carbon disulfide.

Claus and Foecking[2] claim to have reduced acetodurene to durylmethylcarbinol by means of zinc dust. Their evidence was the carbon-hydrogen composition of the product, but this does not distinguish between ketone and carbinol. They report the melting point of the carbinol to be 72° which is the same as that of the ketone. No mixture melting point comparison was reported. We repeated the work of Claus and Foecking and found the product made by their method to be unchanged acetodurene. The reduction of acetodurene with lithium aluminum hydride gives a product melting at 51–52°. That our product is durylmethylcarbinol was confirmed by the preparation of its *p*-nitrobenzoate and α-*N*-naphthylcarbamate derivatives.

An attempt to distil durylmethylcarbinol resulted in dehydration. A small amount of vinyldurene was obtained as distillate but the major product was the nondistilled residue from which two products (m.p. 152–153° and 103–104°) were obtained by fractional crystallization. We believe these compounds to be the *meso* and *dl* modifications of α,α′-didurylidiethyl ether (V). Both show infrared absorption at 9.2μ characteristic of the aliphatic ether linkage and their carbon-hydrogen analyses and molecular weights agree with the ether formula.

Fuson and co-workers[3] have shown that hindered ketones such as acetomesitylene, acetodurene, and acetoisodurene form stable trihalo derivatives upon treatment with alkaline hypohalite. Likewise diacetodurene (VI) forms bis(trichloroaceto)durene by the action of sodium hypochlorite and this product is unchanged by refluxing with 2*N* sodium hydroxide for twenty-four hours.

Diacetodurene is easily reduced to the corresponding diol (VII) by means of lithium aluminum hydride. Aluminum isopropoxide–isopropyl alcohol, however, was unable to accomplish this reduction.

Acetodurene was isomerized[4] to acetoprehnitene (IX) by means of aluminum chloride. The reaction of acetoprehnitene with semicarbazide hydrochloride gave two products. One of these was the semicarbazone (m.p. 211–212°) reported by Baddeley and Pendleton;[4] the other melted at 182–183°. The carbon hydrogen ratios, molecular weights, and infrared spectra suggest that these compounds are the *syn* and *anti* forms of acetoprehnitene semicarbazone.

The carbinols were dehydrated to the corresponding vinyl compounds by distillation in the presence of potassium acid sulfate.

EXPERIMENTAL

The freezing points are corrected; the latter were determined by extrapolation of freezing curves, temperatures being measured by certified platinum resistance thermometer and G-2 Mueller bridge. Purities were estimated from the shapes of the freezing curves. Boiling points and melting points are uncorrected.

Acetylation of durene (A). To a stirred slurry (5°) of 587 g. (4.4 moles) of aluminum chloride in 1200 ml. of carbon tetrachloride was added 314 g. (4.0 moles) of acetyl chloride during 1 hr. After stirring for 1 hr., a solution of 536 g. (4.0 moles) of durene in 1200 ml. of carbon tetrachloride was added at 0–10° during 1 hr.; the mixture was stirred at 0–10° for 2 hr., at 20–30° for 2 hr., then poured into a mixture of 480 ml. of concentrated hydrochloric acid and 1400 g. of crushed ice. The carbon tetrachloride layer was washed with 5% sodium carbonate followed by water, dried, and concentrated. Distillation of the residue yielded 565 g. (80%) of crude acetodurene (b.p. 129–140°/9 mm., m.p. 69–72°). Redistillation of a 1120-g. batch of acetodurene through a 53-plate column at 5/1 reflux ratio yielded 978 g. (69%) of acetodurene (b.p. 128–132°/9 mm., f.p. 71.74°, purity 96.5 ± 0.5 mole %). Part of this material was crystallized from petroleum ether (b.p. 30–60°) to give an 88% recovery of acetodurene; f.p. 72.92°, purity 99.2 ± 0.2 mole % (lit. b.p. 129–131°/10 mm., m.p. 73°[5]).

Acetylation of durene (B). To a stirred slurry (25°) of 800 ml. of carbon disulfide, 168 g. (1.25 moles) of durene, and

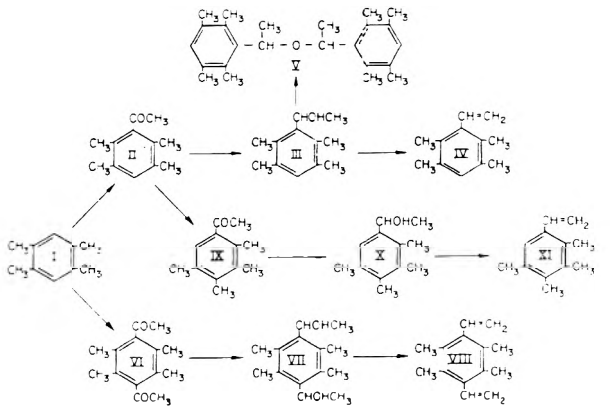
(1) G. Perrier, *Ber.*, **33**, 815 (1900); W. J. Heintzelman and B. B. Corson, *J. Org. Chem.*, **22**, 25 (1957).

(2) A. Claus and C. Foecking, *Ber.*, **20**, 3097 (1887).

(3) A. R. Gray, J. T. Walker, and R. C. Fuson, *J. Am. Chem. Soc.*, **53**, 3494 (1931).

(4) G. Baddeley and A. G. Pendleton, *J. Chem. Soc.*, 807 (1952).

(5) L. I. Smith and C. Guss, *J. Am. Chem. Soc.*, **59**, 804 (1937).



587 g. (4.4 moles) of anhydrous aluminum chloride was added 245 g. (2.4 moles) of acetic anhydride during 1 hr. The mixture was stirred and refluxed for 3 hr., then cooled and poured into a mixture of 230 ml. of concentrated hydrochloric acid and 700 g. of crushed ice. The carbon disulfide layer was washed successively with water, 5% sodium carbonate, and water, dried and concentrated. The concentrate was distilled to yield 123 g. (56%) of crude acetodurene (b.p. 125–131°/10 mm.) and a residue. The latter was crystallized from ether to yield 31 g. (14%) of diacetoisodurene, m.p. 121–122° (lit. m.p. 121[35]).

Anal. Calcd. for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.21; H, 8.50.

Durylmethylcarbinol. Acetodurene (200 g., 1.14 moles) in 1200 ml. of dry ether was added during 1.5 hr. to a stirred solution of 43.2 g. (1.14 moles) of lithium aluminum hydride in 1200 ml. of dry ether. After stirring and refluxing for 3 hr. the mixture was cooled to 20°, diluted with 400 ml. of cold water, and poured into 3 l. of 10% sulfuric acid. The ether layer was washed with 5% sodium carbonate followed by water, dried, and concentrated under reduced pressure to yield 195 g. (96%) of durylmethylcarbinol, m.p. 50–52°. Recrystallization from petroleum ether raised the m.p. to 51–52°.

Anal. Calcd. for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.81; H, 10.40.

α-Durylethyl-p-nitrobenzoate. Colorless needles from methanol, m.p. 109–110°.

Anal. Calcd. for $C_{19}H_{21}NO_4$: C, 69.70; H, 6.47; N, 4.28. Found: C, 70.01; H, 6.61; N, 4.40.

α-Durylethyl-α-naphthylcarbamate. Colorless crystals from methanol, m.p. 151–152°.

Anal. Calcd. for $C_{23}H_{25}NO_2$: N, 4.03. Found: N, 4.30.

α,α'-Diduryl diethyl ether. An attempt to distill 290 g. of durylmethylcarbinol gave 50 g. of distillate (b.p. 108–110°/11 mm.) which solidified and 196 g. of residue. The distillate was crystallized from petroleum ether to give vinyldurene; melting point and mixture melting point with an authentic sample 34–35°. The distillation residue was separated by fractional crystallization (first from methanol, finally from methyl ethyl ketone) into two components, (A), m.p. 152–153° (37 g.) and (B) m.p. 103–104° (12 g.). Both of these compounds showed infrared absorption at 9.2 μ indicative of an aliphatic ether.

Anal. Calcd. for $C_{24}H_{34}O$: C, 85.15; H, 10.12; mol. wt., 338. Found (I): C, 85.11; H, 10.21; mol. wt., 334. Found: (B); C, 85.06; H, 10.17; mol. wt., 340.

Vinyldurene. A mixture of 185 g. (1.04 moles) of durylmethylcarbinol, 6 g. of fused potassium acid sulfate, and 5 g. of *t*-butylcatechol was heated from 190 to 250° at 20 mm. for 1 hr. during which 145 g. of distillate (b.p. 110–150°) was collected. The product was distilled through a 20-cm. Vigreux column to yield 133 g. of crude vinyldurene which was redistilled through a 53-plate column at 5/1 reflux ratio to yield 102 g. (62%) of vinyldurene; b.p. 104°/7.5 mm., f.p. 34.10°, purity 99.85 ± 0.05 mole %. Infrared scanning revealed bands corresponding to a terminal vinyl group at 10.1 and 10.9 μ.

Anal. Calcd. for $C_{12}H_{16}$: C, 89.94; H, 10.06. Found: C, 90.02; H, 10.10.

α,β-Dibromoethyldurene. To an ice cooled solution of 11.6 g. (0.073 mole) of vinyldurene in 115 ml. of dry ether was added 11.5 g. (0.073 mole) of bromine during 0.5 hr. and the mixture was stirred for 2 hr. Ether was evaporated under reduced pressure to yield 21.3 g. (92%) of dibromide. Crystallization from petroleum ether gave colorless crystals, m.p. 93.5–94.5°.

Anal. Calcd. for $C_{12}H_{16}Br_2$: Br, 49.94. Found: Br, 50.00.

Diacetodurene.[6] To a stirred slurry (25°) of 4500 ml. of carbon disulfide and 900 g. (6.72 moles) of aluminum chloride was added 375 g. (4.77 moles) of acetyl chloride during 0.5 hr.; after stirring for 1 hr., 150 g. (1.11 moles) of durene was added and the mixture was stirred and refluxed for 1 hr. Carbon disulfide was stripped off and the residue poured into a mixture of 300 ml. of concentrated hydrochloric acid and 4500 g. of crushed ice. The aqueous suspension was digested on the steam bath for 3 hr., cooled, and filtered. The solid was washed with water and crystallized from methanol to yield 89 g. (37%) of diacetodurene, m.p. 182.5–183.0° (lit. m.p. 178°[6]).

Bis(trichloroaceto)durene. To a stirred solution of 0.1 mole of potassium hypochlorite in 130 ml. of water at 55° was added 3.3 g. (0.015 mole) of diacetodurene. The mixture was stirred at 55° for 5 hr. followed by 14 hr. at 25°. Excess hypochlorite was destroyed by bisulfite and the mixture was filtered. The precipitate was washed with water, air-dried, and crystallized from ethanol to yield 2.4 g. (36%) of bis(trichloroaceto)durene, m.p. 222–223°.

Anal. Calcd. for $C_{14}H_{12}Cl_6O_2$: C, 39.56; H, 2.85; Cl, 50.05. Found: C, 39.65; H, 3.19; Cl, 50.16.

An attempt to hydrolyze the hexachloro compound by refluxing with 2*N* sodium hydroxide for 24 hr. resulted in a 90% recovery of starting material. No evidence of an acidic product was obtained.

Reaction of diacetodurene with lithium aluminum hydride. A flask containing 19.0 g. (0.50 mole) of lithium aluminum hydride in 2 l. of dry ether was attached to a Soxhlet apparatus containing 54.5 g. (0.25 mole) of diacetodurene. The ether was refluxed for 14 hr. The flask was cooled in ice, 100 ml. of cold water was added, and the mixture was poured into 10% sulfuric acid. Filtration gave a solid which was washed successively with 10% sulfuric acid, 5% sodium carbonate, and water. The ether layer was separated from the filtrate, washed with 5% sodium carbonate followed by water, and dried. The ether was evaporated under reduced pressure to give additional solid which was combined with that obtained by filtration. The yield of bis(α-hydroxyethyldurene) was 47.6 g. (86%), m.p. 220–223°. Recrystallization from chloroform raised the melting point to 222–223°.

Anal. Calcd. for $C_{14}H_{22}O_2$: C, 75.63; H, 9.97. Found: C, 75.78; H, 10.06.

Duryl-di-α-ethyl-di-α-naphthylcarbamate. Colorless crystals, first from chloroform, finally from toluene, m.p. 221.0–222.5° (dec.).

Anal. Calcd. for $C_{36}H_{36}N_2O_4$: N, 5.00. Found: N, 4.98.

Divinyldurene. A mixture of 42 g. (0.19 mole) of crude bis(α-hydroxyethyl)durene, 3 g. of fused potassium acid sulfate, and 2 g. of *t*-butylcatechol was heated from 200 to 250° at 3 mm. during 0.5 hr. and the distillate (b.p. 120–160°/3 mm.) was redistilled to yield 23 g. (65%) of crude divinyldurene (b.p. 114–124°/3 mm.). Redistillation through a 15-cm. Vigreux column gave a fraction (b.p. 114–115°/3 mm.) which after two recrystallizations from methanol melted at 67–68°.

Anal. Calcd. for $C_{14}H_{18}$: C, 90.26; H, 9.74. Found: C, 90.12; H, 10.10.

(6) F. Baum and V. Meyer, *Ber.*, **28**, 3212 (1895); V. Meyer, *Ber.*, **29**, 846 (1896).

Bis(α,β-dibromoethyl)durene. To a stirred ice cooled solution of 9.3 g. (0.05 mole) of divinyldurene in 150 ml. of dry ether was added 16.0 g. (0.10 mole) of bromine during 0.5 hr. After stirring overnight at room temperature the ether was evaporated under reduced pressure to yield 23 g. (91%) of residue. Crystallization, first from cyclohexane, finally from methyl ethyl ketone, gave bis(α,β-dibromoethyl)-durene, m.p. 166–167°.

Anal. Calcd. for $C_{14}H_{18}Br_4$: Br, 63.18. Found: Br, 63.62.

Isomerization of acetodurene to acetoprehnitene. A mixture of 323 g. (1.84 moles) of acetodurene, 645 g. (4.84 moles) of aluminum chloride and 43 g. of sodium chloride was stirred at 90° for 2 hr. The product was poured into a mixture of 500 ml. of concentrated hydrochloric acid and 2 kg. of crushed ice. The organic layer was washed successively with water, 5% sodium carbonate, and water, then dried. The ether was stripped off and the residue distilled to give 290 g. of crude acetoprehnitene (b.p. 125–150°/10 mm.) which was redistilled through a 53-plate column at 5/1 reflux ratio to yield 228 g. of acetoprehnitene; b.p. 141–142°/10 mm., f.p. 11.52°, purity 98.5 ± 0.6 mole % (lit. b.p. 122–124°/8 mm.[4]).

Acetylation of prehnitene. To a stirred mixture (−5°) of 114 g. (0.85 mole) of aluminum chloride and 230 ml. of carbon tetrachloride was added 61 g. (0.78 mole) of acetyl chloride during 30 min. After stirring for 1 hr. a solution of 104 g. (0.78 mole) of prehnitene (f.p. −11.42°; purity 98.6 ± 0.5 mole %) in 230 ml. of carbon tetrachloride was added at a rate such that the temperature did not exceed 0°. The mixture was stirred for 2 hr. at 0° followed by 2 hr. at room temperature, then poured into a mixture of 100 ml. of concentrated hydrochloric acid and 300 g. of crushed ice. The organic layer was washed successively with water, 5% sodium carbonate and water, then dried. Carbon tetrachloride was stripped off and the residue distilled through a 10-cm. Vigreux column. The distillate was redistilled through a 53-plate column at 5/1 reflux ratio to yield 87 g. (64%) of acetoprehnitene; b.p. 137–138°/9 mm., f.p. 10.56°, purity 97.0 ± 1.0 mole %.

Acetoprehnitene semicarbazone. A mixture of 49.2 g. (0.279 mole) of acetoprehnitene (f.p. 11.36°, purity 99.1 ± 0.3 mole %), 41.7 g., 0.374 mole) of semicarbazide hydrochloride, 56.1 g. (0.685 mole) of anhydrous sodium acetate, 208 ml. of ethanol, and 164 ml. of water was refluxed for 3 hr., cooled at 5° for 12 hr., and filtered to yield 16.1 g. (24%) of acetoprehnitene semicarbazone (A), m.p. 211–212° (from ethanol); lit. m.p. 209°.[4] The filtrate was concentrated to 50% of its original volume, cooled to 5°, and filtered to yield 10.7 g. (16%) of an isomeric acetoprehnitene semicarbazone (B), m.p. 182–183° (from carbon tetrachloride).

Anal. Calcd. for $C_{13}H_{19}N_3O$: C, 66.92; H, 8.21; N, 18.01; mol. wt., 233. Found (A): C, 67.01; H, 8.11; N, 17.93; mol. wt., 240. Found (B): C, 67.06; H, 7.99; N, 17.81; mol. wt., 225.

Reaction of acetoprehnitene with lithium aluminum hydride. A solution of 72.3 g. (0.41 mole) of acetoprehnitene in 400 ml. of dry ether was added during 30 min. to a stirred solution of 15.6 g. (0.41 mole) of lithium aluminum hydride in 510 ml. of dry ether. The mixture was stirred and refluxed for 3 hr., cooled to 5°, and 100 ml. of wet ether was added followed by 200 ml. of water. The mixture was poured into 1 l. of 10% sulfuric acid. The ether layer was washed with 5% sodium carbonate followed by water, dried, and concentrated under reduced pressure to yield 66 g. (91%) of prehnitylmethylcarbinol, m.p. 53–55°. Crystallization from petroleum ether raised the m.p. to 54–55°.

Anal. Calcd. for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 81.20; H, 10.56.

α-Prehnitylethyl-α-naphthylcarbamate. Colorless solid, crystallized first from cyclohexane, finally from methanol, m.p. 146–147°.

Anal. Calcd. for $C_{23}H_{25}NO_2$: N, 4.28. Found: N, 4.03.

Vinylprehnitene. A mixture of 390 g. (2.19 moles) of prehnitylmethylcarbinol, 10 g. of fused potassium acid sulfate, and 10 g. of *t*-butylcatechol was heated from 190 to 220° at 20 mm for 1 hr. during which 315 g. of distillate was collected. The product was distilled through a 53-plate column at 2/1 reflux ratio to yield 218 g. (62%) of vinylprehnitene; b.p. 117–118°/10 mm., f.p. −9.88°, purity 94.5 ± 2.0 mole %.

Anal. Calcd. for $C_{12}H_{16}$: C, 89.94; H, 10.06. Found: C, 90.37; H, 9.66.

α,β-Dibromoethylprehnitene. To an ice cooled solution of 17.4 g. (0.11 mole) of vinylprehnitene in 173 ml. of dry ether was added 17.3 g. (0.11 mole) of bromine during 0.5 hr. and the mixture was stirred for 2 hr. Ether was evaporated under reduced pressure to yield 32.8 g. (86%) of dibromide. Crystallization from petroleum ether gave colorless crystals, m.p. 76.5–77.5°.

Anal. Calcd. for $C_{12}H_{16}Br_2$: Br, 49.94. Found: Br, 50.00.

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

Cathodic Reduction of Negatively Substituted Ketones: α-Ketoacids and β-Ketoesters

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The cathodic reduction of α-ketoacids and β-ketoesters has been studied. The α-carboxyl group in α-ketoacids has been found to promote reduction but not pinacol formation compared with a phenyl group. It also has a pronounced effect upon the stereoisomeric identity of the pinacol product, unlike unsubstituted ketones. The carbethoxy group in β-ketoesters inhibits pinacol formation in acid medium and favors hydroxy acid in alkaline medium.

Since it has been shown that the presence of an alpha aryl group in ketones promotes pinacol type reduction by either chemical or electrochemical methods,[1] it was of interest to study the effect of other negative groups such as carboxyl and carbethoxyl groups located in the alpha and beta positions on the course of cathodic reduction.

The reductions were carried out at mercury or mercury plated copper gauze cathodes at constant cathode potential.[2] In general, it was found necessary to use the mercury cathode when the product was insoluble to avoid clogging of the cathode with subsequent loss of current efficiency.

The compounds studied were pyruvic, and benzoylformic acids, ethyl acetoacetate, and ethyl benzoylacetate. Pyruvic acid has previously been reduced electrolytically to lactic acid in aqueous sulfuric acid but no pinacol was reported.[3] In the present work, in addition to lactic acid a small amount of one isomer of dimethyltartaric acid was isolated from reductions in aqueous sulfuric acid. The best yields of the latter product were obtained when the reaction was carried out in aqueous acetic acid or in solutions of pyruvic acid buffered to *p*H 2–6 with ammonia.

Benzoylformic acid was readily reduced in acid, buffered acid, or alkaline media. Maximum yields (50–60%) of the mixed diphenyltartaric acids were obtained in alkaline solution. In addition to the pinacol, a small amount of mandelic acid was isolated from acid reductions. The crude pinacol could be separated into *racemic* and *meso* fractions. Applying the rule of Stern,[4] the *meso* configuration may be tentatively assigned to the higher melting isomer. The *meso* isomer was the principal one formed in alkaline solution while the *racemic* form was the main product in acid solution. The latter isomer appeared to be the one isolated by Schonberg[5] by photochemical reduction of benzoylformic acid. On vacuum sublimation, the *meso* isomer disproportionated to mandelic acid and benzoylformic acid.

Benzoyl cyanide failed to reduce in acid solution. Methyl benzoylacetate was readily reduced in alkaline solution but the yield of dimethyl diphenyltartrate was low due to partial hydrolysis of the esters during the reaction.

Ethyl acetoacetate failed to reduce in either acid or alkaline media at either of the cathodes.

Reduction of ethyl benzoylacetate in acid or buffered acid solutions produced a 1:1 mixture of *racemic* and *meso*-diethyl 3,4-diphenyl-3,4-dihydroxyglutarate in 50–60% yields. However, considerable unreacted starting material was recovered and it was noted that the concentration of the ester in the catholyte had to be about 5% before any reduction would occur at all. Also, addition of the reductant to the catholyte produced a 10–20% rise in the cathode potential instead of the drop that occurred with the α-ketoacids (50%) and acetophenone (30%). Only β-phenyl-β-hydroxypropionic acid was isolated from alkaline reductions.

These results indicate that, under similar conditions the presence of the alpha carboxyl group facilitates reduction (acetone fails to reduce under conditions effective with pyruvic acid) it is not as effective in promoting pinacol formation as a phenyl group.[6] However, it does have a pronounced effect in upsetting the 1:1 ratio of the stereoisomeric pinacols formed in contrast to the beta carbethoxy group and unsubstituted ketones,[7] where the two isomers are formed in about equal amounts. The beta carbethoxyl group not only does not favor pinacol formation but actually inhibits reduction as shown by the rise in cathode potential and recovery of unreacted starting material. The larger yield of pinacol formed from

(1) The method of M. Gomber and W. E. Bachmann [*J. Am. Chem. Soc.*, **49**, 236 (1927)] using magnesium subiodide is effective only on diaryl ketones. Michler's ketone is reduced at a copper cathode [F. Escherich and M. Moest, *Z. Elektrochem.*, **8**, 849 (1902)] while acetone fails to reduce even when the copper cathode is mercury plated (*loc. cit.*).

(2) M. J. Allen and A. H. Corwin, *J. Am. Chem. Soc.*, **72**, 114 (1950).

(3) G. W. Rockwell, *J. Am. Chem. Soc.*, **24**, 719 (1902).

(4) R. Stern, Abstracts of Papers 131st Meeting American Chemical Society, Miami, Fla., April 7–12, 1957.

(5) A. Schonberg, N. Latif, R. Moubasher, and A. Sina, *J. Chem. Soc.*, 1364 (1951).

(6) Compare results of runs 1,2,3 with 4 and 5 Table I. Also note that alkyl aryl ketones frequently give higher pinacol yields[7-14] than benzoylformic acid.

(7) R. E. Juday and W. J. Sullivan, *J. Org. Chem.*, **20**, 617 (1955).

TABLE I

Run	Initial C.d./Cm.[2]	Cathode	Cathode Potential	Electrolyte	Products (% Yield) Pinacol	Alcohol
			Pyruvic Acid			
1	0.018	Cu(Hg)	1.1	H_2SO_4	4	45
2	0.012	Cu(Hg)	1.1	Acetic acid	7	—
3	0.014	Cu(Hg)	0.7	Ammonia *p*H 2–5	11	—
			Benzoylformic Acid			
4	0.0078	Cu(Hg)	0.75	NaOH	60 (mostly *meso*)	—
5	0.0078	Cu(Hg)	0.5	H_2SO_4	20 (mostly *dl*)	7
6	0.0078	Cu(Hg)	0.8	NaOH *p*H 4–6	trace	—
			Ethyl Benzoylacetate			
7	0.058	Cu(Hg)	1.4	NaOH	0	44
8	0.037	Hg	4.2	H_2SO_4	60 1:1 *dl*, *meso*)	0
9	0.037	Hg	6.5	H_2SO_4	61	0
10	0.037	Hg	3.0	HCl	50	0
11	0.037	Hg	3.4	$HClO_4$	35	0

benzoylformic acid in alkaline solution is in agreement with results obtained with other ketones.[7] The failure of ethyl benzoylacetate to form the pinacol in alkaline solution may be due to the fact that reduction of the enolate anion present produces only the alcohol while the pinacol is produced primarily from the keto form.

EXPERIMENTAL

Benzoyl cyanide. The procedure in *Organic Syntheses*[8] was used except that 15 g. of powdered potassium iodide was added to the reaction mixture and the crude product was purified by recrystallization from petroleum ether rather than by fractional distillation.

Benzoylformic acid. Benzoyl cyanide was hydrolyzed using the procedure in *Organic Syntheses*.[9]

Reductions. Apparatus. Reactions were run in a 200-ml. Berzelius beaker using the anode, diaphragm, and cathodes as previously outlined.[7] In addition, a calomel electrode was placed in the cell close to the cathode in order to measure cathode potential. Current was passed through the cell containing all of the components but the reductant until the cathode potential was constant. The reductant was then added and its effect on the cathode potential noted. The potential was then maintained throughout the run by manual adjustment[10] of the current with a rheostat until gassing indicated that the reaction was completed. In general, there was little change in the potential until near the end of the run. All reactions were run between 15° and 25°.

Reduction of pyruvic acid to dimethyltartaric acid and lactic acid. The catholyte contained 90 ml. of water and 7–10 g. of pyruvic acid. In acid reductions 2–4 g. of sulfuric acid or 5–10 g. of acetic acid was added. In buffered solutions enough ammonia was added to maintain the *p*H between 2 and 5 during the reaction. If necessary a small amount of acetic acid could be added near the end of the reaction to keep the solution acidic. Mercury plated copper gauze cathodes were used throughout. The yields obtained in typical runs are summarized in Table I.

The dimethyltartaric acid was first separated as the barium salt. When sulfuric acid was used as electrolyte, an amount of barium hydroxide equivalent to the sulfuric acid was first added and the suspension filtered. Extra barium hydroxide was then added and the product separated. When ammonia was used as buffer, the catholyte was first made alkaline with ammonia, concentrated *in vacuo*, and diluted with alcohol to precipitate the ammonium salt which was then dissolved in water and treated with barium hydroxide. To isolate the free acid, the barium salt was suspended in water and treated with an equivalent amount of sulfuric acid. The suspension was filtered and concentrated to about a 40% solution *in vacuo*. Removal of water was completed in a vacuum desiccator over phosphorus pentoxide. A yield of 6 g. of the acid melting at 174–175° (177–178°[11]) was obtained starting with 9 g. of the ammonium salt. The acid was converted to the dimethyl ester with diazomethane and recrystallized from ligroin, m.p. 50–51.7°.

Anal. Calcd. for $C_8H_{14}O_6$: C, 46.60; H, 6.80. Found: C, 46.72; H, 6.70.

Lactic acid was isolated from the catholyte after removal of the sulfuric acid by evaporating and distilling the residue *in vacuo*. It was identified by conversion to the *p*-bromophenacyl ester, m.p. 110–112°.

Reduction of benzoylformic acid to diphenyltartaric acid and mandelic acid. The catholyte contained 90 ml. of water, 5–7 g. of benzoylformic acid, and 2 g. of sulfuric acid or 3–5 g. of sodium hydroxide. In buffered solution enough base was added to neutralize partially the benzoylformic acid. Mercury plated copper gauze cathodes were used as yields with the mercury cathode were very low. The yields of products obtained in typical runs are summarized in Table I.

When sulfuric acid was used as electrolyte, it was first removed by adding excess barium chloride and filtering. The filtrate was neutralized with sodium hydroxide and a 100% excess of barium hydroxide added to precipitate the barium salts of the diphenyltartaric acids. When sodium hydroxide was used as electrolyte the barium hydroxide could be added directly. The barium salts were suspended in water and treated with excess 20% hydrochloric acid. The precipitated acid was filtered, washed with water, and dried *in vacuo* over phosphorus pentoxide. The isomers could be separated by fractional crystallization of the sodium salts from dilute sodium chloride solution. The product from acid reduction contained about 90% of the *dl* isomer, m.p. 153.5–155°(155°).[5]

(8) T. S. Oakwood and C. A. Weissberger, *Org. Syntheses*, **Coll. Vol. 3,** 112 (1955).

(9) T. S. Oakwood and C. A. Weissberger, *Org. Syntheses*, **Coll. Vol. 3,** 114 (1955).

(10) R. Pasternak, *Helv. Chim. Acta*, **31,** 753 (1948) and private communication.

(11) C. Bottinger, *Ber.*, **25,** 397 (1892).

Anal. Calcd. for $C_{16}H_{14}O_6$: C, 63.58; H, 4.63. Found: C, 63.42; H, 4.74.

The product from alkaline reduction contained about 90% of the *meso* isomer, m.p. 217–219°.

Anal. Calcd. for $C_{16}H_{14}O_6$: C, 63.58; H, 4.63. Found: C, 63.39; H, 4.75.

The acids were converted to the dimethyl esters with diazomethane and recrystallized from alcohol. The ester of the *dl* acid melted at 119–121°.

Anal. Calcd. for $C_{18}H_{18}O_6$: C, 65.45; H, 5.45. Found: C, 65.60; H, 5.30.

The ester of the *meso* acid melted at 151.5–153°.

Anal. Calcd. for $C_{18}H_{18}O_6$: C, 65.45; H, 5.45. Found: C, 65.35; H, 5.48.

The catholyte from the acid reduction of benzoylformic acid was treated with an equivalent amount of barium hydroxide to remove sulfate. The solution was evaporated to dryness *in vacuo* and the residue treated with a little warm water. Filtration followed by concentration produced 0.4 g. of mandelic acid, m.p. 116–117°. The yield of pinacol was 1.9 g.

Pyrolysis of meso-diphenyltartaric acid. The acid vacuum sublimed with decomposition at 140–160°/0.1 mm. The product was dissolved in ether and most of the ether evaporated. On standing partial crystallization occurred. The solid was filtered and washed with ligroin, ether. It melted at 116–117° and showed no depression when mixed with *dl*-mandelic acid. The residual oil was treated with dinitrophenylhydrazine. The dinitrophenylhydrazone melted at 194–196° and showed no depression when mixed with benzoylformic acid dinitrophenylhydrazone.

Reduction of ethyl acetoacetate. Aqueous alcohol solutions of the ester with sodium hydroxide or sulfuric acid added as electrolyte were used. No reduction products were isolated with either of the cathodes.

Reduction of ethyl benzoylacetate to diethyl β,β'-diphenyl-3,3'-dihydroxyadipate and β-phenyl-β-hydroxypropionic acid. The catholyte contained 50 ml. of alcohol, 25 ml. of dioxane, 30 ml. of water, and 3–4 g. of acid. Sulfuric, hydrochloric, and perchloric acids were used with sulfuric and hydrochloric giving the best results. A minimum of 5 g. of ester was necessary to get reduction with 14–15 g. being used in most runs. In buffered acid, the catholyte consisted of 75 ml. of acetic acid, 40 ml. of water, and 5 g. of sodium acetate. In alkaline medium the catholyte contained 45 ml. of alcohol, 45 ml. of water, and 4 g. of sodium hydroxide. The ester was mostly hydrolyzed during the run, so the product recovered was the acid rather than the ester. Because of the insolubility of the pinacol it was necessary to use the mercury cathode in all acid reductions. Since no pinacol was formed in alkaline solution the mercury plated copper gauze cathode was used. The yields of products obtained in typical runs are summarized in Table I, and are based on reacted starting material.

dl- and *meso*-Diethyl β,β'-diphenyl-β,β'-dihydroxyadipate were isolated from the catholyte from the acid reductions by filtration. The filtrate was concentrated *in vacuo* and the residue distilled *in vacuo* to recover the unreacted ester. The residue from the distillation crystallized and was added to the yield of pinacol after washing with a little alcohol. The *dl* isomer was separated from the *meso* by dissolving in cold benzene. It was purified by recrystallizing from ethanol. A yield of 3.1 g., m.p. 131–135° (137°)[12] was obtained from 6.5 g. of the mixed pinacols. The residue left after the treatment with cold benzene was recrystallized from butanone to give 3.2 g. of the *meso* isomer, m.p. 166–168.5° (168°).[12]

The catholyte from the alkaline reduction was acidified with hydrochloric acid and evaporated *in vacuo* until all of the alcohol was removed. The residue was extracted twice with ether and the ether solution evaporated to dryness. The residue was decolorized with Norit and recrystallized from benzene. A yield of 4.2 g. of β-phenyl-β-hydroxypropionic acid, m.p. 89–91°(92–93°),[13] was obtained from 11 g. of starting material. No pinacol could be isolated from the reaction mixture.

MISSOULA, MONT.

(12) E. Beschke, *Ann.*, **384**, 143 (1911).

(13) E. Erlenmeyer and G. Hilgendorff, *Biochem. Z.*, **35**, 140.

(14) S. Swann, P. Ambrose, R. Dale, R. Rowe, H. Ward, H. Kerfman, and S. Axelrod, *Trans. Electrochem. Soc.*, **85**, 231 (1944).

[CONTRIBUTION FROM THE ENTOMOLOGY RESEARCH DIVISION, AGRICULTURAL RESEARCH SERVICE, U. S. DEPARTMENT OF AGRICULTURE]

Preparation of the Chrysanthemumates of 6-Bromo- and 6-Chloropiperonyl Alcohols

W. F. BARTHEL[1] AND B. H. ALEXANDER

Received December 12, 1957

An over-all synthesis in high yield of two esters, 6-bromo- and 6-chloropiperonyl chrysanthemumates which have high toxicity to insects and low toxicity to mammals, is reported.

The search for new insecticides of low mammalian toxicity is part of the research program of the Entomology Research Division. Of particular interest in this respect have been esters of chrysanthemumic acid[2,3] and about two hundred of these have been prepared at the Beltsville, Md., laboratory and tested for insecticidal activity at the Orlando, Fla., laboratory of the Division. This paper reports the preparation of the 6-bromo- and 6-chloropiperonyl chrysanthemumates[4] which are among the most effective of these compounds.

(1) Present address: Plant Pest Control Laboratory, U. S. Department of Agriculture, P. O. Box 989, Gulfport, Miss.

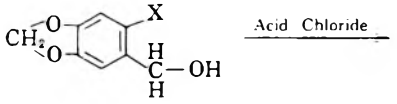
(2) Y. L. Chen and W. F. Barthel, *J. Am. Chem. Soc.*, **75**, 4287 (1953); U. S. Dept. of Agr., ARS-33-23 (1956).

(3) W. F. Barthel and B. H. Alexander, U. S. Dept. of Agr., ARS-33-42 (1957).

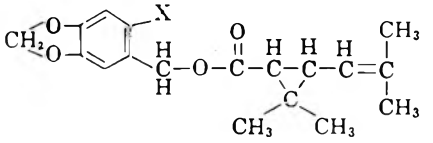
(4) W. F. Barthel, B. H. Alexander, P. G. Piquett, and J. B. Gahan, U. S. patent pending.

The esters are highly toxic to both mosquito larvae and house flies *Musca domestica* (L.); they have, though, an extremely low order of mammalian toxicity.[5]

The chrysanthemumates were prepared by treating the halogenated piperonyl alcohols (II)[6] with chrysanthemumic acid chloride. II was

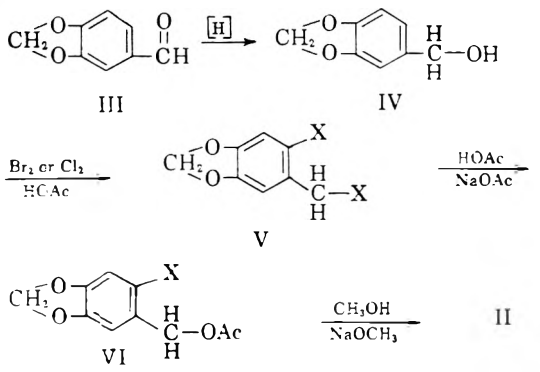


II (X = Cl or Br)



I

initially prepared by the following series of reactions, in which each intermediate was isolated and characterized:



When larger quantities of I were needed for additional testing, a high yield four-step synthesis was devised without the isolation of intermediates. As a check on the purity and identity of II, the alcohols were prepared by way of the aldehyde through lithium aluminum hydride reduction.

Also described is another procedure for the synthesis of I (X = Cl) by transesterification in which II (X = Cl) was treated with ethyl chrysanthemumate[7] with sodium metal as the catalyst.

EXPERIMENTAL

6-Bromopiperonyl bromide (V, X = Br).[6] Bromine (24 ml.) in glacial acetic acid (60 ml.) was slowly added to piperonyl alcohol (60 g.) in glacial acetic acid (120 ml.), with mechanical stirring and cooling (15–25°). Crystallization occurred on standing overnight at 25°, and the crude crystals (84 g.) melted at 91–93°. After recrystallization from methyl alcohol, the melting point was 92–93° (lit. 94°); yield 75%.

Acetate of 6-bromopiperonyl alcohol (VI, X = Br). The above bromide (74 g.), anhydrous sodium acetate (41 g.), and glacial acetic acid (300 ml.) were refluxed for 4 hr. The solution was poured into ice and water and kept at 5° for several hours. The crude product (66 g.) melted at 80–82°, and after one recrystallization from ethyl alcohol melted at 81–82°; yield 96%.

Anal. Calcd. for $C_{10}H_9BrO_4$: Br, 29.3%. Found: Br, 29.7%.

6-Bromopiperonyl alcohol (II, X = Br). (A) The above acetate (50 g.) and 2*N* sodium methylate in methanol (100 ml.) were refluxed for 4 hr. and then poured into cold water. The crude crystals (43 g.) melted at 89–90°, and after recrystallization from ethyl alcohol melted at the same temperature (lit. 90°); yield was quantitative.

(B) 6-Bromopiperonal (40 g.), prepared according to Orr *et al.*,[8] was reduced with lithium aluminum hydride (9 g.) by the extraction method of Nystrom and Brown.[9] The crude product (35 g.), after recrystallization from ethyl alcohol, melted at 89–90°; yield 90%. A mixture of these crystals with those from (A) melted at 89–90°.

6-Chloropiperonyl alcohol (II, X = Cl). The lithium aluminum hydride (4.6 g.) reduction of 6-chloropiperonal (74 g.) gave 6-chloropiperonyl alcohol (72 g.) in 96% yield; m.p. 66–69° (lit.[6] 73–74°).

Anal. Calcd. for $C_8H_7ClO_3$: Cl, 18.84%. Found: Cl, 18.97%.

6-Bromopiperonyl chrysanthemumate (I, X = Br). To a stirred solution of bromopiperonyl alcohol (23 g.), low-boiling (30°–40°) petroleum ether (200 ml.), and dry pyridine (9 ml.) maintained at about 45°, chrysanthemumic acid chloride (19 g.) was slowly added and the mixture was stirred for several hours. After remaining at 25° for 18 hr., the mixture was washed with 5% hydrochloric acid, 5% sodium hydroxide, and cold water. The petroleum ether layer was dried over anhydrous sodium sulfate and the solvent was removed. The crude product (32 g., yield 80%) was distilled: b.p. 183–200°/1.1 mm., n_D^{25} 1.5483.

Anal. Calcd. for $C_{15}H_{21}BrO_4$: Br, 20.69%. Found: Br, 20.61%.

6-Chloropiperonyl chrysanthemumate (I, X = Cl) was prepared from 6-chloropiperonyl alcohol in the same manner as the bromo compound; yield 73%; b.p. 184–206°/0.7 mm., n_D^{25} 1.5378.

Anal. Calcd. for $C_{18}H_{21}ClO_4$: Cl, 10.53%. Found: Cl, 10.45%.

4-Step synthesis of 6-bromopiperonyl chrysanthemumate (I, X = Br). A 3-liter flask, equipped with stirrer, dropping funnel, thermometer, and drying tube, and arranged so that it could be cooled with a water bath or heated electrically, was charged with 300 g. of piperonyl alcohol and 1 liter of glacial acetic acid. With the temperature maintained at 15–20°, 340 ml. of bromine was added dropwise over 4 hr. and the mixture was allowed to stand overnight. Then 250 g. of anhydrous sodium acetate was added. The dropping funnel was replaced with a reflux condenser, and the solution heated to reflux. The mixture was mechanically stirred to prevent bumping during the 4-hr. reflux period, then cooled and poured into ice water with stirring. Stirring was continued for 1 hr. while granular crystals formed. The crystals were filtered, pressed dry, and transferred to a 5-liter flask containing 2 liters of methanol. Then 200 g. of sodium hydroxide dissolved in 500 ml. of water was added. The mixture was refluxed for 3 hr. and poured into 4 liters of ice water with vigorous mechanical stirring. After 1 hr. of stirring the crystals were filtered and transferred to a 5-liter flask equipped with a water separator and reflux con-

(5) Personal communication from Dr. Anthony M. Ambrose, Army Environmental Health Lab, Army Chemical Center, Md.

(6) R. G. Naik and T. S. Wheeler, *J. Chem. Soc.*, 1780 (1938).

(7) A sample of the ethyl ester of D,L-*cis*,*trans*-chrysanthemumic acid was furnished by Fairfield Chemical Div., Food Machinery and Chemical Corp., Baltimore, Md.

(8) A. M. B. Orr, R. Robinson, and M. M. Williams, *J. Chem. Soc.*, 946 (1917).

(9) R. F. Nystrom and W. G. Brown, *J. Am. Chem. Soc.*, 49, 2548 (1947).

denser. Two liters of benzene were added, and the mixture was refluxed until no more water separated.

The flask was then equipped with a mechanical stirrer, reflux condenser, and dropping funnel. Dry pyridine (200 ml.) was added, followed by dropwise addition of 342 g. (1.8 mole) of chrysanthemumic acid chloride. After the mixture had stood overnight, water was added to dissolve the pyridine hydrochloride. The upper benzene layer was washed consecutively with dilute hydrochloric acid, saturated sodium bicarbonate solution, and saturated sodium chloride solution, and then dried with sodium sulfate overnight. The benzene was removed and the residue distilled under high vacuum. A small forerun was obtained and then the main fraction; b.p. 183–200°/1.1 mm., n_D^{25} 1.5496; yield 593 g. (78% based on piperonyl alcohol).

The over-all 4-step synthesis for the chloro derivative was similar to the bromo except that chlorination took place at 50° instead of 15–25°.

6-Chloropiperonyl acetate (VI, X = Cl). Hydrolysis of V (X = Cl) in glacial acetic acid and anhydrous sodium acetate in the usual manner gave VI in 83% yield melting at 84–85°.

Anal. Calcd. for $C_{10}H_9ClO_4$: Cl, 15.48%. Found: Cl, 15.17%.

6-Chloropiperonyl alcohol in 93% yield was prepared from this acetate by sodium hydroxide hydrolysis in methanol; m.p. (from ethanol) 69–70°, mixed melting point with that prepared by reduction of 6-chloropiperonal 69–70.5°.

Anal. Calcd. for $C_8H_7ClO_3$: Cl, 18.84%. Found: Cl, 18.97%.

6-Chloropiperonyl ester of chrysanthemumic acid by transesterification (I, X = Cl). One molar amount of ethyl chrysanthemumate[7] and 6-chloropiperonyl alcohol were heated to 150° in a flask, equipped with a Dean-Starke trap and thermometer. Shortly after addition of 0.25 g. of sodium, ethanol began to distil. When this liberation of ethanol ceased, another 0.25 g. of sodium was added and more alcohol liberated. This procedure was repeated (about eight additions), the temperature being maintained between 150–160°, until the theoretical quantity of ethanol was collected. The mixture was then cooled and dissolved in ether. The solution was washed with dilute hydrochloric acid, saturated sodium bicarbonate, saturated sodium chloride solution, and finally dried over sodium sulfate. After removal of the ether and some forerun of unreacted ethyl chrysanthemumate and 6-chloropiperonyl alcohol, the product distilled; b.p. 155–171°/0.2 mm., n_D^{25} = 1.5375; yield 65%.

BELTSVILLE, MD.

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

Preparation of Some *N*-Substituted Phenothiazines in Tetrahydrofuran

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Tetrahydrofuran was found to be an excellent solvent for the preparation of some *N*-substituted phenothiazine derivatives. 10-(*n*-Decyl)phenothiazine, 10-(*n*-octadecyl)phenothiazine, and 10-(*o*-bromobenzyl)phenothiazine were prepared in high yields using this technique. The sulfoxides and sulfones of 10-(*n*-decyl)phenothiazine and 10-(*n*-octadecyl)phenothiazine were also prepared in very good yields.

N-Substitutions of phenothiazine can be accomplished by a number of techniques. These include the sealed tube reaction such as was used for the preparation of 10-phenothiazinecarbonyl chloride using a mixture of phenothiazine and phosgene in toluene;[1–3] reactions between phenothiazine and a halogen compound in a solvent such as toluene or xylene using a basic condensing agent (*e.g.*, sodium carbonate or sodium hydroxide) and a copper powder catalyst as in the preparation of 10-(*p*-methoxyphenyl)phenothiazine from phenothiazine, *p*-iodoanisole, potassium carbonate, and copper powder in refluxing xylene;[4] reactions similar to that just described in the absence of solvent as in the preparation of 10-phenylphenothiazine by heating a mixture of iodobenzene, phenothiazine, sodium carbonate, and copper powder;[4] and reactions between 10-sodiophenothiazine and an appropriate halide in anhydrous liquid ammonia as in the preparation of 10-ethylphenothiazine from 10-sodiophenothiazine (prepared from phenothiazine and sodium amide in liquid ammonia) and ethyl bromide.[5,6]

10-(*n*-Decyl)phenothiazine and 10-(*n*-octadecyl)-phenothiazine have both been prepared in low yield (10% and 20%, respectively).[7] In these preparations, a mixture of phenothiazine, sodium carbonate, copper powder, and the appropriate alkyl bromide was heated for 11–12 hr. at 180°. Purification was accomplished by extraction with ether, vacuum distillation of the residue after removal of the ether, and, in the case of the *n*-octadecyl derivative, recrystallization of the distilled material from absolute ethanol.

Champaigne[8] prepared 10-(*n*-decyl)phenothiazine

(1) N. Fraenkel, *Ber.*, 18, 1843 (1885).
(2) S. Paschkowezky, *Ber.*, 24, 2905 (1891).
(3) R. Dahlbom, *Acta Chem. Scand.*, 7, 879 (1953).
(4) H. Gilman, P. R. Van Ess, and D. A. Shirley, *J. Am. Chem. Soc.*, 66, 1214 (1944). For general references on the chemistry of phenothiazine see the excellent article by S. P. Massie, *Chem. Revs.*, 54, 797 (1954).
(5) H. Gilman, R. D. Nelson, and J. F. Champaigne, Jr., *J. Am. Chem. Soc.*, 74, 4205 (1952).
(6) H. Gilman, R. K. Ingham, J. F. Champaigne, Jr., J. W. Diehl, and R. O. Ranck, *J. Org. Chem.*, 19, 560 (1954).
(7) H. Gilman and D. A. Shirley, *J. Am. Chem. Soc.*, 66, 888 (1944).
(8) J. F. Champaigne, Jr., M.S. thesis, Iowa State College (1952).

in a high crude yield (86.7%) using the liquid ammonia procedure. However, he was unable to get this in a pure form, the product being contaminated with phenothiazine and an unidentified red component even after attempted chromatographic purification (using benzene as the solvent and eluent on a column of activated alumina) and distillation of the chromatographed material. Champaigne[8] also attempted the preparation of the 10-*n*-octadecyl derivative by the addition of either a toluene or xylene solution of *n*-octadecyl bromide to a mixture of 10-sodiophenothiazine in liquid ammonia. This work was unsuccessful.

In the work reported herein, both 10-(*n*-decyl)-phenothiazine and 10-(*n*-octadecyl)phenothiazine were prepared successfully by several techniques. Using the liquid ammonia procedure, 10-(*n*-decyl)-phenothiazine was prepared pure in yields between 60 and 80%. The procedure used was similar to that described by Champaigne[8] except that a greater concentration (five to ten times as great) of 10-sodiophenothiazine in ammonia was used, and petroleum ether (b.p. 60–70°) was substituted for benzene in the chromatographic purification. The chromatographed material was also vacuum-distilled to give a product free of phenothiazine and the red component.

Experiments utilizing ether as a solvent for the *n*-decyl bromide and liquid ammonia as a solvent or carrier for the 10-sodiophenothiazine showed no outstanding advantage over the above technique except, perhaps, a slight advantage in yield of the final product. The same purification procedure [chromatography using petroleum ether (b.p. 60–70°) as the solvent and eluent followed by vacuum distillation] was used here.

A definite advantage was indicated by the use of tetrahydrofuran alone as a solvent for this reaction. Using this technique, a tetrahydrofuran solution of *n*-decyl bromide was added to a solution of 10-sodiophenothiazine in tetrahydrofuran to give an 87% yield of pure product. The purification required only simple vacuum distillation of the crude product.

10-(*n*-Octadecyl)phenothiazine was also prepared successfully by several techniques. Using the liquid ammonia procedure and adding molten *n*-octadecyl bromide under conditions of high concentration a 17% crude yield or 12.9% pure yield of product was obtained. Variations of this procedure, which are described under Experimental, gave lower yields of product.

The use of various solvents for the *n*-octadecyl bromide and addition of these solutions to 10-sodiophenothiazine in liquid ammonia enabled yields of product ranging between 40 and 50%. Solvents used were ether, ethylene glycol dimethyl ether, and tetrahydrofuran. When pentane was used as a solvent for the halogen compound, a yield of less than 5% was obtained. In this series of experiments, the order of addition did not seem to be critical.

When the tetrahydrofuran procedure was used, a yield of 91% of pure 10-(*n*-octadecyl)phenothiazine was obtained. The use of ether in place of tetrahydrofuran was not adequate, a lower yield (estimated) being obtained.

Since tetrahydrofuran had been so successful in the above alkylations, it was investigated for the preparation of other *N*-substituted phenothiazine derivatives. 10-Phenylphenothiazine failed to form either at room temperature or in refluxing tetrahydrofuran when iodobenzene was used. Even when the halogen was activated by a nitro group, as in *o*- and *p*-iodonitrobenzene, no product was obtained. No 10-(2-pyridyl)- or 10-(2-quinolyl)phenothiazine formed in tetrahydrofuran when using 2-bromopyridine and 2-chloroquinoline, respectively. Compounds having a very reactive halogen such as triphenylmethyl chloride, *o*-bromobenzyl chloride, and *p*-nitrobenzyl bromide were also investigated. The *o*-bromobenzyl chloride gave a high crude yield of 10-(*o*-bromobenzyl)phenothiazine, but the material was very difficult to purify. The triphenylmethyl chloride gave an unidentified product while the *p*-nitrobenzyl bromide gave a product tentatively indentified as *p,p'*-dinitrobibenzyl.

Tetrahydrofuran was selected as a solvent for the *N*-alkylations and attempted *N*-arylations because of its higher polarity (1.68 Debye units)[9] compared to ether (1.22 Debye units).[10] In the mixed solvent systems, ether-ammonia has shown a definite advantage over such combinations as pentane-ammonia, toluene-ammonia,[3] and xylene-ammonia.[3] These hydrocarbon solvents are much lower in polarity than ether, ranging from zero Debye units for pentane[11] to 0.1 to 0.58 Debye units for xylene.[12] The tetrahydrofuran did not show any advantage over ether in the mixed solvent technique but did show a decided advantage over ether when used as a solvent for both the 10-sodiophenothiazine and the halogen compound in the preparation of 10-(*n*-octadecyl)phenothiazine. This could possibly be attributed to the higher polarity of tetrahydrofuran over ether, but since compounds such as *o*-iodo- and *p*-iodonitrobenzene failed to react with 10-sodiophenothiazine it is believed that this solvent has little effect on the leaving group or at least not appreciably more than ether itself.

(9) L. G. Wesson, *Tables of Electric Dipole Moments*, The Technology Press, Massachusetts Institute of Technology, Cambridge, Mass., 1949, p. 21.

(10) L. G. Wesson, *Tables of Electric Dipole Moment*, The Technology Press, Massachusetts Institute of Technology, p. 22.

(11) L. G. Wesson, *Tables of Electric Dipole Moments*, The Technology Press, Massachusetts Institute of Technology, p. 25.

(12) L. G. Wesson, *Tables of Electric Dipole Moments*, The Technology Press, Massachusetts Institute of Technology, p. 40.

The success of tetrahydrofuran in the preparation of 10-(*n*-decyl)-phenothiazine and 10-(*n*-octadecyl)-phenothiazine has been attributed partially to the increased solubility of 10-sodiophenothiazine and the halogen compound in this solvent as compared to ammonia, pentane, xylene, toluene, and ether. Both *n*-decyl bromide and *n*-octadecyl bromide are solid in liquid ammonia. If they were liquid in liquid ammonia they would probably give nearly quantitative yields of their corresponding phenothiazine derivatives since their reactivity is comparable to that of ethyl bromide.[13] Ethyl bromide remains liquid in liquid ammonia, or may dissolve to some extent, and gives a quantitative yield of 10-ethylphenothiazine.[5,6] When using molten undiluted *n*-decyl bromide or *n*-octadecyl bromide most of the reaction in liquid ammonia must occur before the halogen compound solidifies. This is supported by those experiments involving the preparation of 10-(*n*-octadecyl)phenothiazine in which both molten and finely ground *n*-octadecyl bromide were used. The first of these gave a 17% crude yield and the latter, less than 5% crude yield.

Both the 10-(*n*-decyl)phenothiazine and 10-(*n*-octadecyl)phenothiazine were oxidized to the monoxides and dioxides. These oxidations were accomplished by well known procedures, the monoxides being formed by oxidation with 30% hydrogen peroxide in refluxing ethanol and the dioxides by treatment with 30% hydrogen peroxide in warm (80°), glacial acetic acid. The preparation 10-(*n*-octadecyl)phenothiazine-5-oxide in 53% yield using hydrogen peroxide in ethanol has been reported previously.[7] The use of a greater concentration of unoxidized product in absolute ethanol and an extension of the reaction time in the work reported here, provided a 96% yield of product. The other oxidized compounds, 10-(*n*-decyl)phenothiazine-5-oxide and -5,5-dioxide, and 10-(*n*-octadecyl)phenothiazine 5,5-dioxide, have not been reported previously. In the preparation of 10-(*n*-decyl)phenothiazine-5-oxide, the use of a higher concentration of unoxidized compound and hydrogen peroxide also proved advantageous.

10-(*n*-Decyl)phenothiazine-4-carboxylic acid was prepared by the reductive metalation of 10-(*n*-decyl)phenothiazine-5-oxide with *n*-butyllithium followed by carbonation and hydrolysis. A similar procedure has been described for the preparation of 10-ethylphenothiazine-4-carboxylic acid from 10-ethylphenothiazine-5-oxide.[6] The 10-(*n*-decyl) derivative was obtained in a lower yield than was reported for 10-ethylphenothiazine-4-carboxylic acid.

(13) C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, Cornell University Press, Ithaca, N. Y., 1953, p. 316.

EXPERIMENTAL[14]

10-(n-Decyl)phenothiazine. (*a*) *In anhydrous liquid ammonia.* Two and six-tenths grams (0.11 g.-atom) of sodium was added to 150 ml. of anhydrous liquid ammonia contained in a flask equipped with a Dewar-type Dry Ice condenser. Immediately after the first few pieces of sodium were added, a crystal of ferric nitrate was introduced as a catalyst. Stirring was continued for approximately 1 hr. or until the gray color of the sodium amide was very evident. Twenty grams (0.1 mole) of phenothiazine was then added and stirring was continued for another hour during which time the color of the reaction became orange-yellow. Thirty-three grams (0.15 mole) of *n*-decyl bromide was added and stirring was continued for 6 hr. The ammonia was evaporated and the residue was extracted with petroleum ether (b.p. 60–70°). This extract was chromatographed on a column of activated alumina, the column being eluated with additional petroleum ether (b.p. 60–70°). The solvent was stripped from the eluate and the material which remained was vacuum distilled to give 28.5 g. (84%) of a yellow oil boiling at 175–180° (0.5 mm.). The reported boiling point for this compound is 183–185° (0.5 mm.).

Other similar experiments in which the concentration of 10-sodiophenothiazine was varied (0.1 mole in 100 ml. to 200 ml. of liquid ammonia) gave yields ranging from 60–80%.

The use of high speed agitation showed no advantages.

(*b*) *Using ether as a solvent for the halogen compound.* One-tenth mole of 10-sodiophenothiazine in 150 ml. of liquid ammonia was prepared as in the experiment above. A solution of 33 g. (0.15 mole) of *n*-decyl bromide in 100 ml. of ether was added and agitation was continued for 6 hr. The solvents were then evaporated and the residue was extracted with petroleum ether (b.p. 60–70°). This extract was chromatographed on a column of activated alumina and the column was eluted with additional petroleum ether (b.p. 60–70°). The solvent was stripped from the eluate and the remaining material was vacuum-distilled to give 28.5 g. (84%) of pure product boiling at 175–180° (0.5 mm.).

Using this same procedure but with high speed agitation, and shorter reaction times, (1, 2, and 3 hr.) yields of about 75% were obtained.

(*c*) *Using tetrahydrofuran.*[15] One-tenth mole of 10-sodiophenothiazine was prepared in 150 ml. of liquid ammonia by the procedure described in part (*a*) of this section. One hundred and fifty milliliters of tetrahydrofuran was then added and the ammonia was permitted to evaporate. Before all of the ammonia had escaped, the contents were placed under an atmosphere of nitrogen and kept this way until the reaction was complete. A solution of 33 g. (0.1 mole) of *n*-decyl bromide in 150 ml. of tetrahydrofuran was added over a period of 15–20 min. and stirring was continued at room temperature for 12 hr. The tetrahydrofuran was removed by distillation and the remaining residue was extracted with benzene. This was filtered, the benzene was distilled from the filtrate, and the oily compound which remained was subjected to vacuum distillation. Twenty-nine and one-half grams (86.5%) of material boiling at 175–180° (0.5 mm.), n_D^{26} 1.5853, d_{25}^{25} 1.0442 was obtained.

Anal. Calcd. for $C_{22}H_{29}NS$: MR_D, 110.84. Found: MR_D, 111.57.

10-(n-Octadecyl)phenothiazine. (*a*) *In liquid ammonia.* One-tenth mole of 10-sodiophenothiazine was prepared in the usual manner by the addition of 20 g. (0.1 mole) of phenothiazine to 0.11 mole of sodium amide (prepared from 2.6 g. of sodium using a ferric nitrate catalyst) in 150 ml. of liquid ammonia. Fifty grams (0.15 mole) of molten *n*-

(14) All melting points reported herein are uncorrected.

(15) The tetrahydrofuran which was used in these experiments was Eastman Kodak Co. White Label. This was dried and further purified by refluxing over sodium for several hours and then distilling just prior to use.

octadecyl bromide was added and stirring with a high-speed counter-rotating agitator was continued for 3 hr. The ammonia was evaporated and the residue was extracted with petroleum ether (b.p. 60–70°). This extract was filtered and then chromatographed on a column of activated alumina, the column being eluted with additional petroleum ether (b.p. 60–70°). Evaporation of the solvent from the eluate left 7.5 g. (17%) of crude material melting at 42–44°. Recrystallization of this from an ethanol-water system gave 5.8 g. (12.9%) of white material having a melting point of 52–52.5° and which showed no depression in melting point when mixed with an authentic sample (53°).[7]

A few variations, which gave lower yields, were made in this procedure. These included the addition of 10-sodiophenothiazine in liquid ammonia to a dispersion of *n*-octadecyl bromide in liquid ammonia (5% crude yield), 10-sodiophenothiazine in liquid ammonia added to molten (40–50°) *n*-octadecyl bromide (10% crude yield), and ground (28 mesh) *n*-octadecyl bromide added to 10-sodiophenothiazine in liquid ammonia (5% crude yield).

(*b*) *Using various solvents for the halogen compound.* One-tenth mole of 10-sodiophenothiazine was prepared as above in 150 ml. of liquid ammonia. A solution of 50 g. (0.15 mole) of *n*-octadecyl bromide in 150 ml. of ether was added and stirring was continued for 7 hr. A four-bladed propeller-type agitator run at about 1200 r.p.m. was used for this. Evaporation of the solvents left 25 g. (55%) of crude material which on recrystallization from an ethanol-water system gave 11.5 g. (25%) of material melting at 42–43°.

When 100 ml. of liquid ammonia was used for the 10-sodiophenothiazine and 200 ml. of ether for the halogen compound, 32.8 g. (72.5%) of crude material melting at 40–43° was obtained. Recrystallization of this from an ethanol-water system gave a 40% yield of pure material melting at 53°. When an inverse addition was employed with these same amounts of material, a 53% yield of white product melting at 53.5° resulted. A higher ratio of ether to ammonia offered no advantages.

When the ammonia-10-sodiophenothiazine mixture was added to an *n*-pentane solution of *n*-octadecyl bromide a 6% crude yield of product was obtained. Using this inverse addition with tetrahydrofuran as a solvent for the halogen compound, a 36% yield of pure material was obtained and with ethylene glycol dimethyl ether, again with the inverse addition, a 49% yield of pure material resulted. When normal addition was made using ethylene glycol dimethyl ether as a solvent for the halogen compound, a 54% yield of material melting at 53–54° was produced.

(*c*) *Using tetrahydrofuran.* One-tenth mole of 10-sodiophenothiazine was prepared in 150 ml. of liquid ammonia using the procedure described in part (*a*) of this section. One hundred and fifty milliliters of tetrahydrofuran was added and the ammonia was permitted to evaporate. Before all of the ammonia had escaped, the contents of the flask were placed under an atmosphere of nitrogen. When the reaction mass had warmed to room temperature, a solution of 50 g. (0.15 mole) of *n*-octadecyl bromide in 150 ml. of tetrahydrofuran was added over a period of 2 hr. and stirring was continued for 32 hr., the temperature being maintained at 20–25°. The tetrahydrofuran was removed by distillation and the residue was extracted with benzene. This extract was filtered and the benzene was stripped from the filtrate. The excess *n*-octadecyl bromide was removed by vacuum distillation. The remaining undistilled portion weighed 47 g. and had a melting point of 44–45°. Recrystallization of this from an ethanol-water system gave 40.5 g. (90%) of white material having a melting point of 53–54°. A repeat of this experiment gave the same results.

Refluxing the tetrahydrofuran solution of the reactants showed no advantages.

When ether was substituted for tetrahydrofuran as a solvent for both the halogen compound and the sodiophenothiazine a much cruder product was formed. This was not purified, but it is estimated that the amount of pure product which would have formed would have been between 50–60%.

10-(o-Bromobenzyl)phenothiazine. One-tenth mole of 10-sodiophenothiazine was prepared by adding 20 g. (0.1 mole) of phenothiazine to 0.11 mole of sodium amide (prepared from 2.6 g. of sodium using a ferric nitrate catalyst) in 100 ml. of liquid ammonia. One hundred and fifty milliliters of tetrahydrofuran was added and the ammonia was permitted to evaporate. Before all of the ammonia had escaped, the contents of the flask were put under an atmosphere of nitrogen. A solution of 27 g. (0.132 mole) of *o*-bromobenzyl chloride in 150 ml. of tetrahydrofuran was added to the 10-sodiophenothiazine at room temperature over a period of 15 min. and stirring was continued for a period of 6 hr. at this same temperature. The reaction mass was filtered and the solvent removed by distillation. Thirty-six grams of a brown viscous oil remained.

Attempted chromatographic purification by passing a benzene solution of the crude material through a column of activated alumina, elution with benzene and evaporation of the solvent from the eluate left a viscous oil which failed to solidify. Recrystallization of a portion of this from an ethanol-water system gave material having a melting point range of 91–93° but the crystal formation was poor.

Further purification of the chromatographed material by vacuum distillation was also inadequate since a large portion of the material tended to pyrolyze. Material boiling at 190–200° (0.005 mm.) was collected. This was also resinous in nature and crystallized with difficulty from an ethanol-water system. Two recrystallizations from this solvent system gave a white product melting at 90–92°. The infrared spectrum showed an absorption band characteristic of *ortho* disubstitution and had no absorption band in the region characteristic of N–H.

Anal. Calcd. for $C_{19}H_{15}BrNS$: S, 8.71. Found: S, 8.99, 9.01.

A sulfur analysis was also run on some of the chromatographed material to determine how its quality compared to the recrystallized material. The analysis was quite marginal but it did indicate that it was the desired material. This quality material was produced in 88% yield.

Anal. Calcd. for $C_{19}H_{15}BrNS$: S, 8.71. Found: S, 9.20, 9.34.

10-(n-Decyl)phenothiazine-5-oxide. Ten grams (0.0295 mole) of 10-(*n*-decyl)phenothiazine was dissolved in 600 ml. of refluxing absolute ethanol. Twenty-five milliliters (0.24 mole) of 30% hydrogen peroxide was added and stirring was continued at reflux for 6 hr. Three hundred and fifty milliliters of the solution was removed by distillation and the remainder was poured into 1250 ml. of water previously heated to 75°. After refrigeration, 10.1 g. (93%) of material crystallized from the solution. This was recrystallized from an ethanol-water system to give 9.2 g. (90%) of white material melting at 97–98°. Another recrystallization from this same solvent system failed to increase the melting point.

The infrared spectrum showed the characteristic sulfoxide absorption band.

Anal. Calcd. for $C_{22}H_{29}NOS$: S, 9.02. Found: S, 8.87, 9.00.

In another experiment in which a greater concentration of reactants was employed (102 g. of 10-(*n*-decyl)phenothiazine in 2250 ml. of absolute ethanol oxidized with 93 ml. of 30% hydrogen peroxide followed by removal of 1500 ml. of solvent and pouring into 3700 ml. of water previously heated to 75°) 99 g. (93%) of material melting at 97–98° and 5 g. (5%) of material melting at 91–92° were obtained, this last portion after concentration of the filtrate.

10-(n-Octadecyl)phenothiazine-5-oxide. Ninety grams (0.2 mole) of 10-(*n*-octadecyl)phenothiazine was dissolved in 2000 ml. of refluxing absolute ethanol. Sixty milliliters (0.59 mole) of 30% hydrogen peroxide was added and stirring was continued at reflux for 5 hr. Fifteen hundred milliliters of the solvent was removed by distillation and the remaining undistilled portion was poured into 2500 ml. of water previously heated to 80°. Upon cooling to room temperature,

92 g. (98%) of cream colored material having a melting point range of 90–95° separated. Recrystallization of this from an ethanol-water system gave 90 g. (96%) of material melting at 95–96°. Additional recrystallizations failed to raise the melting point further. A mixture melting point with an authentic specimen (98°)[7] showed no depression. A 53% yield of this material made by a somewhat similar procedure has been reported.[7]

10-(n-Decyl)phenothiazine-5,5-dioxide. Seventeen grams (0.05 mole) of 10-(*n*-decyl)phenothiazine was dissolved in 290 ml. of glacial acetic acid at 70°. Sixteen milliliters (0.154 mole) of 30% hydrogen peroxide was added causing the formation of a deep red color. Stirring was continued for 1.5 hr. at 80° after which an additional 5 ml. (0.048 mole) of 30% hydrogen peroxide was added. This caused no apparent change in the reaction. One hundred and ninety milliliters of the solvent was removed by distillation. Upon cooling, 13.5 g. (73%) of pink-brown material having a melting point of 93–95.5° separated. Recrystallization of this from an ethanol-water system produced 12.1 g. (67%) of tan material having a melting point of 95.5–96.5°. Additional recrystallization did not raise the melting point.

The infrared spectrum showed the characteristic sulfone absorption bands.

Anal. Calcd. for $C_{22}H_{29}NO_2S$: S, 8.65. Found: S, 8.49, 8.50.

An additional 4.7 g. of a brown semisolid material was recovered by dilution of the acetic acid filtrate from the reaction mixture with water. No effort was made to purify this.

10-(n-Octadecyl)phenothiazine-5,5-dioxide. Twenty-two and one-half grams (0.05 mole) of 10-(*n*-octadecyl)phenothiazine was dissolved in 300 ml. of glacial acetic acid at 80°. Fifteen milliliters (0.147 mole) of 30% hydrogen peroxide was added and the reaction was stirred for 1.5 hr., the temperature being maintained at 80°. An additional 10 ml. (0.098 mole) of 30% hydrogen peroxide was added, causing no change in the reaction. Upon cooling to room temperature, 22 g. (91.5%) of cream colored material melting at 93–93.5° separated. Recrystallization of this from absolute ethanol failed to increase the melting point. The infrared spectrum showed an absorption band characteristic of a sulfone.

Anal. Calcd. for $C_{30}H_{45}NO_2S$: S, 6.63. Found: S, 6.64, 6.71.

10-(n-Decyl)phenothiazine-4-carboxylic acid. Seventeen and one-quarter grams (0.05 mole) of 10-(*n*-decyl)phenothiazine-5-oxide was suspended in 250 ml. of anhydrous ether under an atmosphere of nitrogen. The suspension was cooled to −20° by means of a Dry Ice–acetone bath and 0.05 mole of *n*-butyllithium[16] in 45 ml. of ether was added at such a rate as to maintain the temperature at −20°. After stirring for 2 hr. at −20° another 0.1 mole of *n*-butyllithium in 90 ml. of ether was added and the mixture was permitted to warm to 0° where it was maintained for 4 hr. The reaction mass was then poured jet-wise into an agitated Dry Ice-ether slurry. After this mixture had warmed to room temperature, the ether was extracted with 100 ml. (0.262 mole) of 10% sodium hydroxide in several portions. Acidification of the basic extract with hydrochloric acid caused the separation of a yellow oil which gradually solidified on standing. This weighed 7 g. (36%) and had a melting point of 124–125°. Recrystallization of this from glacial acetic acid gave 6.2 g. (32%) of bright yellow material melting at 128–129°. Additional recrystallizations failed to increase the melting point. The infrared spectrum showed characteristic absorptions bands for the carbonyl group and 1,2,3 trisubstitution.

Anal. Calcd. for $C_{23}H_{29}NO_2S$: S, 8.36. Found: S, 8.21, 8.33.

The sodium salt of this compound was prepared by adding an excess of 10-(*n*-decyl)phenothiazine-4-carboxylic acid to a solution of dilute sodium hydroxide. When the maximum amount of material had dissolved, the solution was filtered and the filtrate was allowed to evaporate slowly. Yellow plate-like crystals having a melting point of 253–254° formed. A flame test indicated the presence of sodium.

Acknowledgment. We wish to thank Mr. E. Miller Layton, Jr., of the Ames Laboratory of the Institute for Atomic Research for the determination of the infrared spectra.

AMES, IOWA

(16) H. Gilman, J. A. Beel, C. G. Brannen, M. W. Bullock, G. E. Dunn, and L. S. Miller, *J. Am. Chem. Soc.*, **71**, 1499 (1949).

[CONTRIBUTION FROM THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH]

A New Synthesis of 10-(3-Dimethylaminopropyl)-2-(trifluoromethyl)phenothiazine Hydrochloride[1] and 7-Substituted Derivatives[2]

K. FLOREY AND A. R. RESTIVO

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The zinc salt of 2-amino-4-(trifluoromethyl)benzenethiol reacted with 2,4-dinitrochlorobenzene to give 2-amino-4-(trifluoromethyl)-2′,4′-dinitrodiphenylsulfide. The formamido derivative of the latter was cyclized *via* the Smiles Rearrangement to 7-nitro-2-(trifluoromethyl)phenothiazine. By alkylation with dimethylaminopropyl chloride, 10-(3-dimethylaminopropyl)-7-nitro-2-(trifluoromethyl)phenothiazine was obtained. Reduction to the 7-amino analog and reductive deamination *via* the diazonium compound led to 10-(3-dimethylaminopropyl)-2-(trifluoromethyl)phenothiazine in 35% over-all yield. The diazotization of aminophenothiazines is discussed.

The current interest in 10-(3-dimethylaminopropyl)-2-(trifluoromethyl)phenothiazine (VIII) as an ataractic agent[3] prompted us to seek new synthetic approaches to this compound.

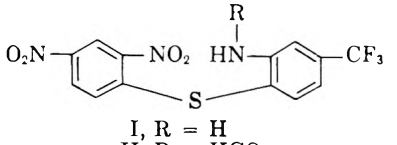
VIII has been synthesized in two laboratories[4,5] by alkylation of 2-(trifluoromethyl)phenothiazine (V). V had been prepared by Smith[6] by thionation of 3-(trifluoromethyl)diphenylamine which led to

(1) The Olin Mathieson Chemical Corp. trademark of this compound is VESPRIN.

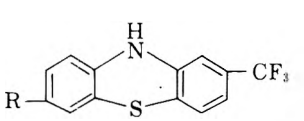
(2) Presented at the 132nd Meeting of the American Chemical Society, New York, September 1957.

a mixture of 2-(trifluoromethyl)phenothiazine (V) in 45% yield and its undesired isomer 4-(trifluoromethyl)phenothiazine in 35% yield. 2-(Trifluoromethyl)phenothiazine has also been synthesized in an unambiguous fashion by Roe and Little[7] *via* the Smiles Rearrangement of 2-formamido-2′nitro-5′-(trifluoromethyl)diphenylsulfide in 59% yield.

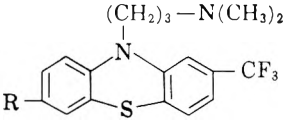
Starting with 2-amino-4-(trifluoromethyl)benzenethiol, the synthesis described in this paper leads to VIII in a 35% over-all yield without the formation of isomers and, furthermore, furnishes means of obtaining 7-substituted derivatives of VIII.



I, R = H
II, R = HCO



III, R = NO_2
IV, R = NH_2
V, R = H



VI, R = NO_2
VII, R = NH_2
VIII, R = H
IX, R = Cl

The zinc salt of 2-amino-4-(trifluoromethyl)-benzenethiol[8] was treated with sodium methylate and 2,4-dinitrochlorobenzene.[9] The resulting 2-amino-4-(trifluoromethyl)-2′,4′-dinitrodiphenylsulfide (I) (85% yield) was converted to its *N*-formamido compound (II) in 90% yield by refluxing in 90% formic acid. II was then cyclized *via* the Smiles Rearrangement[10] to 7-nitro-2-(trifluoromethyl)-phenothiazine (III) in 85% yield. The high yield obtained in this reaction was undoubtedly due to the presence of the second nitro group which facilitated both rearrangement and ring closure. Alkylation of III with dimethylaminopropyl chloride in diethylene glycol dimethyl-ether in the presence of sodamide or sodium hydride proceeded to 10-(3-dimethylaminopropyl)-7-nitro-2-(trifluoromethyl)phenothiazine (VI) in 85% yield. With xylene or toluene as solvents, only erratically low yields were obtained. The hydrochloride of VI was reduced with iron and calcium chloride in 75% ethanol to 7-amino-10-(3-dimethylaminopropyl)-2-(trifluoromethyl)phenothiazine (VII) in 90% yield and recovered as the dihydrochloride. However, isolation of the latter is unnecessary to carry out the next step. Therefore, VII was treated *in situ* with sodium nitrite and hydrochloric acid at 0° and then refluxed for 90 min. The base of 10-(3-dimethylaminopropyl)-2-(trifluoromethyl)-phenothiazine (VIII) was obtained in 70% yield by distillation of the reaction mixture.

The ease with which V could be deaminated was gratifying. Only a few examples of diazotization of phenothiazine derivatives are mentioned in the literature[11] and these have given varying results. The first diazotization described is that of Kehrmann and Vessely[12] who diazotized 3-aminophenothiazine which was then coupled with resorcinol.

A successful reductive deamination has been reported by Krishna and Jain[13] who converted 3-aminophenothiazine to phenothiazine. Baltzly, Harfenist, and Webb,[14] on the other hand, did not succeed in removing the amino group of 7-amino-3-bromophenothiazine by diazotization and reduction.

Successful Sandmeyer reactions have been carried out by Gilman and co-workers[15] who converted 3-amino-10-ethyl-phenothiazine-5-dioxide to 3-chloro-10-ethyl-phenothiazine-5-dioxide in low yield, and by Antonov[16,17] who converted 2-aminophenothiazine-5-dioxide and its *N*-methyl derivative to the corresponding 2-chloro compounds, the latter in 42% yield, the highest yield reported in the literature for any of these diazotiaztion reactions.

When VII was subjected to the Sandmeyer reaction, 7-chloro-10-(3-dimethylaminopropyl)-2-(trifluoromethyl)phenothiazine (IX) was obtained in 35% yield.

Furthermore, 7-amino-2-(trifluoromethyl)phenothiazine (IV), obtained from III by reduction, was deaminated to 2-(trifluoromethyl)phenothiazine (V), albeit in 18% yield. This low yield can be attributed to the fact that the ring-nitrogen is un-

(3) The tranquilizing activity of 10-(3-dimethylaminopropyl)-2-(trifluoromethyl)phenothiazine hydrochloride was first reported by J. C. Burke, H. L. Yale, G. L. Hassert, and J. P. High and by J. J. Piala, J. P. High, K. Greenspan, and J. C. Burke at the 1956 Meeting of the American Society for Pharmacology and Experimental Therapeutics at French Lick Springs, Ind., November 8–10, 1956. For later literature, see *Monographs on Therapy of The Squibb Institute for Medical Research*, 2, 1957.

(4) P. N. Craig, E. A. Nodiff, J. J. Lafferty, and G. E. Ullyot, *J. Org. Chem.*, **22**, 709 (1957).

(5) H. L. Yale, F. Sowinski, and J. Bernstein, *J. Am. Chem. Soc.*, **79**, 4375 (1957).

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

(7) A. Roe and W. L. Little, *J. Org. Chem.*, **20**, 1577 (1955).

(8) A. I. Kiprianov and L. M. Yagupolskii, *Zhur. Obshcheĭ Khim.*, **22**, 2209 (1952) as reported in *Chem. Abstr.*, **47**, 4769 (1953).

(9) *Cf.* R. W. Bost, J. O. Turner, and R. D. Norton, *J. Am. Chem. Soc.*, **54**, 1985 (1932).

(10) *Cf.* J. F. Bunnet and R. E. Zahler, *Chem. Revs.*, **49**, 362 (1951).

(11) *Cf.* S. P. Massie, *Chem. Revs.*, **54**, 797 (1954).

(12) F. Kehrmann and O. Vessely, *Ann.*, **332**, 64 (1902).

(13) S. Krishna and M. S. Jain, *Proc. 15th Indian Sci. Cong.*, 153 (1928), as reported in *Chem. Abstr.*, **25**, 3001 (1931).

(14) R. Baltzly, M. Harfenist, and F. J. Webb, *J. Am. Chem. Soc.*, **61**, 2673 (1946).

(15) H. Gilman, R. K. Ingham, J. F. Champaigne, Jr., J. W. Diehl, and R. O. Ranck, *J. Org. Chem.*, **19**, 560 (1954).

(16) D. S. Antonov, *Bull. inst. chim. ac. bulgare sci.*, **2**, 97 (1953) as reported in *Chem. Abstr.*, **49**, 6267 (1955).

(17) D. S. Antonov and E. Karakasheva, *Bull. inst. chim. ac. bulgare sci.*, **2**, 113 (1953) as reported in *Chem. Abstr.*, **49**, 5442 (1955).

protected, leading to side reactions, since nitrous acid was taken up when 2-(trifluoromethyl) phenothiazine (V) was subjected to the conditions of the diazotization reaction. Neither starting material (V) nor any other defined product could be isolated.

These findings, taken together with those of previous investigators, make it apparent that when the ring-nitrogen is protected by alkylation diazotization of aminophenothiazines proceeds without inherent difficulty. However, it should also be pointed out that of the possible replacements of the diazonium group only the substitution by hydrogen (reductive deamination) and chlorine (Sandmeyer Reaction) have been reported in the literature. It may be significant that our attempts to prepare the corresponding hydroxyl, methoxyl, and ethoxyl compounds from VII resulted only in deamination to VIII. It is not clear whether the inability to effect these replacements is characteristic of phenothiazine diazonium compounds in general, or is governed by the influence of ring substituents such as the trifluoromethyl group in VII. This would have to be made the subject of a much broader study.

EXPERIMENTAL[18]

2-Amino-4-(trifluoromethyl)-2′,4′-dinitrodiphenylsulfide (I). At room temperature and under an atmosphere of nitrogen, a slurry of 900 g. of the zinc salt of 2-amino-4-(trifluoromethyl)benzenethiol in 8 liters of methanol was treated with a solution of 216 g. of sodium methylate in 2 l. of dry methanol to form the sodium salt.

The solution of the sodium salt was then added to a solution of 810 g. of 2,4-dinitrochlorobenzene in methanol and the mixture was agitated and refluxed in an atmosphere of nitrogen for 0.5 hr. Then 5 l. of water were added to the hot solutions and, after a cooling period, the crystals of 2-amino-4-(trifluoromethyl)-2′,4′-dinitrodiphenylsulfide, m.p. 170–175°, were collected in 85% yield. By recrystallization from ethanol the melting point was raised to 180–183°.

Anal. Calcd. for $C_{13}H_8F_3N_3O_4S$: N, 11.70; S, 8.92. Found: N, 11.90; S, 9.29.

2-Formamido-4-(trifluoromethyl)-2′,4′-dinitrodiphenylsulfide (II). One kilogram of 2-amino-4-(trifluoromethyl)-2′,4′-dinitrodiphenylsulfide was refluxed in 10 l. of 90% formic acid for one hour. Twenty-three liters of water were added to the cooled solution and the crystals of 2-formamido-4-(trifluoromethyl)-2′,4′-dinitrodiphenylsulfide (II), m.p. 168–170°, were collected in 90% yield. Recrystallization from chloroform raised the melting point to 172–174°.

Anal. Calcd. for $C_{14}H_8F_3N_3O_5S$: N-formyl 7.49; N, 10.85. Found: N-formyl 7.06; N, 10.89.

7-Nitro-2-(trifluoromethyl)phenothiazine (III). At room temperature and in an atmosphere of nitrogen, 950 g. of 2-formamido-4-(trifluoromethyl)-2′,4′-dinitrodiphenylsulfide in 9.5 l. of dry acetone were treated with 2.5 l. of *N* ethanolic NaOH. The mixture was refluxed for 45 min. Addition of 10 l. of warm water caused precipitation of dark red crystals of 7-nitro-2-(trifluoromethyl)phenothiazine, m.p. 205–210° (dec.) in 85% yield.

Anal. Calcd. for $C_{13}H_7F_3N_2O_2S$: C, 50.00; H, 2.25; N, 8.97. Found: C, 50.31; H, 2.16; N, 9.04.

(18) Melting points were taken on the Fischer-Johns apparatus and are uncorrected.

10-(3-Dimethylaminopropyl)-7-nitro-2-(trifluoromethyl)-phenothiazine (VI). To equimolar amounts of sodium amide and 3-dimethylaminopropyl chloride in 500 ml. of diethylene glycol dimethylether were added 100 g. of 7-nitro-2-(trifluoromethyl)phenothiazine in 500 ml. of the same solvent. The mixture was stirred and heated at 135° for 2 hr. under a blanket of nitrogen. The cooled solution was filtered from insoluble material and acidified with hydrogen chloride. The hydrochloride of 10-(3-dimethylaminopropyl)-7-nitro-2-(trifluoromethyl)phenothiazine, m.p. 235–240° (dec.), was collected in 85% yield. By recrystallization from ethanol, the melting point was raised to 240–245° (dec.).

Anal. Calcd. for $C_{18}H_{18}F_3N_3O_2S{\cdot}HCl$: C, 49.83; H, 4.41; Cl, 8.17; N, 9.69. Found: C, 50.06; H, 4.35; Cl, 8.19; N, 9.44.

7-Amino-10-(3-dimethylaminopropyl)-2-(trifluoromethyl)-phenothiazine (VII). A mixture of 100 g. of 10-(3-dimethylaminopropyl)-7-nitro-2-(trifluoromethyl)phenothiazine hydrochloride, 320 g. reduced iron powder, and 17 g. of calcium chloride in 2 l. of 75% ethanol was agitated and refluxed for 2 hr. The mixture was made strongly alkaline and filtered. The filtrate was either used for reductive deamination (see step VI) or the ethanol was removed. The residue was then taken up in benzene, washed with water, and the crude dihydrochloride of 7-amino-10-(3-dimethylaminopropyl)-2-(trifluoromethyl)phenothiazine was precipitated in 90% yield by addition of hydrogen chloride. By repeated recrystallization from isopropyl alcohol a melting point of 168–170° was obtained.

Anal. Calcd. for dihydrochloride $C_{18}H_{20}F_3N_3S{\cdot}2HCl$: C, 49.09; H, 5.04; N, 9.54; Cl, 16.10. Found: C, 49.02; H, 5.04; N, 9.18; Cl, 15.56.

10-(3-Dimethylaminopropyl)-2-(trifluoromethyl)phenothiazine (VIII). The alkaline filtrate from the previous step was brought to pH 6 with concentrated hydrochloric acid and a further 480 ml. of 2*N* hydrochloric acid was added. The solution was cooled to 0°, and 16.0 g. of sodium nitrite in 80 ml. of water was added. The mixture was stirred at 0° for 30 min., and then refluxed for 90 min. After the ethanol was distilled off, the residual aqueous solution was made strongly alkaline, and extracted with benzene. The benzene extract was washed with water, and then the benzene removed *in vacuo*. The base of VIII was obtained in 70% yield by fractionation of the residue: n_D^{23} 1.5780; b.p. 160–165° at 0.7 mm. Both VIII and its hydrochloride were identical with authentic material.[5]

7-Chloro-10-(3-dimethylaminopropyl)-2-(trifluoromethyl)-phenothiazine (IX). To 120 g. of 7-amino-10-(3-dimethylaminopropyl)-2-(trifluoromethyl)phenothiazine dihydrochloride in 700 ml. of 1.5*N* hydrochloric acid was added a solution of 19.0 g. of sodium nitrite in 100 ml. of water at 0°. A wet filter cake of cuprous chloride was prepared by filtration of a mixture of a solution of 136 g. of $CuSO_4{\cdot}5H_2O$ and 36 g. of sodium chloride in 440 ml. of water with a solution of 29 g. of sodium bisulfite and 19 g. of sodium hydroxide in 220 ml. of water. To the filter cake in a solution of 290 ml. of 6*N* hydrochloric acid, the diazotization mixture was added at 0–5°C. Then 1.5 l. of water were added and the mixture was heated to 80° with agitation for 2 hr. The mixture was then made alkaline and extracted with benzene. The benzene layer was dried, the benzene distilled off *in vacuo*, and the residue fractionated to yield 36.0 g. (35%) of a fraction with a boiling point of 160–165° at 70 *u*; n_D^{25} 1.5880. Twenty three grams of this material in 250 ml. of anhydrous ether was treated with ethereal hydrochloric acid to give 24.8 g. of 7-chloro-10-(3-dimethylaminopropyl)-2-(trifluoromethyl)phenothiazine, m.p. 208–210°. On recrystallization from isopropyl alcohol, the melting point was raised to 210–212°.

Anal. Calcd. for $C_{18}H_{18}F_3ClN_2S{\cdot}HCl$: C, 51.07; H, 4.52; N, 6.62; Cl, 16.75. Found: C, 51.00; H, 4.52; N, 6.50; Cl, 16.57.

7-Amino-2-(trifluoromethyl)phenothiazine (IV). In a solution of 300 ml. of 90% isopropyl alcohol, 17.8 g. of 7-nitro-2-

(trifluoromethyl)phenothiazine was reduced by refluxing for 2 hr. in the presence of 32 g. of reduced iron powder and 1 ml. of concentrated hydrochloric acid. The mixture was made alkaline and filtered hot. The product was isolated from the refrigerated filtrate in 85% yield and recrystallized from toluene, m.p. 235–240° (dec.).

Anal. Calcd. for $C_{13}H_9F_3N_2S$: C, 55.31; H, 3.21; N, 9.93. Found: C, 56.03; H, 3.23; N, 9.93.

2-(Trifluoromethyl)phenothiazine (V). A solution of 4.9 g. of 7-amino-2-(trifluoromethyl)phenothiazine in 120 ml. of isopropyl alcohol and 35 ml. of 2*N* hydrochloric acid was cooled to 5° and treated with a solution of 1.2 g. of sodium nitrite in 10 ml. of water. The mixture was held at 5–10° for 1 hr. and then refluxed for 16 hr., after which it was made alkaline, cooled to 25°, and diluted with 250 ml. of water. The precipitate was recrystallized from toluene to give 850 mg. (18%) of product with m.p. 185–187° and infrared spectrum identical to that of authentic 2-(trifluoromethyl)-phenothiazine.

Anal. Calcd. for $C_{13}H_8F_3NS$: C, 58.42; H, 3.02; N, 5.24. Found: C, 58.73; H, 3.44; N, 5.21.

Acknowledgment. The microanalyses were carried out by Mr. T. Alicino and his associates. The authors are furthermore indebted to Dr. H. L. Yale and Dr. J. Bernstein for ideas and discussions stimulating this investigation.

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[COMMUNICATION NO. 1912 FROM THE KODAK RESEARCH LABORATORIES, EASTMAN KODAK CO.]

2-Substituted-1,3,4-oxa- and thia-diazoline-5-thiones

MAXIMO BARON AND CHARLES V. WILSON

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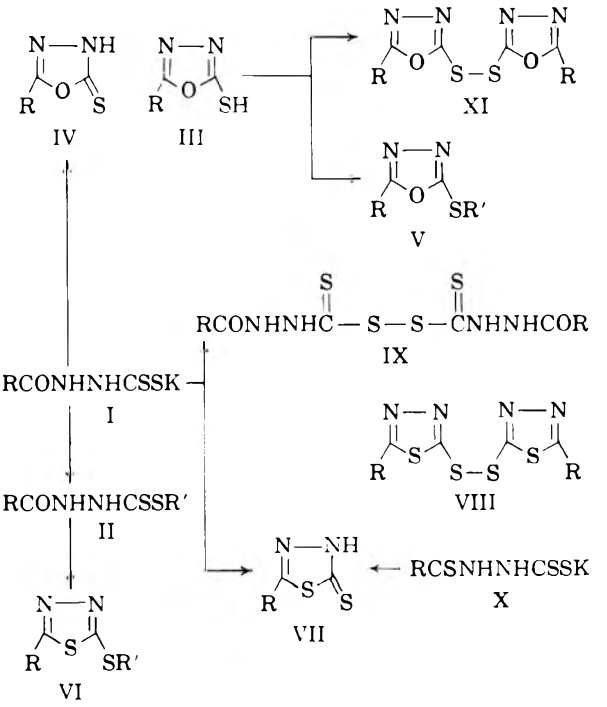
Potassium acyl or aroyldithiocarbazates are cyclized in cold (0–10°) concentrated sulfuric acid to thiadiazolinethiones. At higher temperatures, some disulfide is also formed. Mild oxidation of potassium benzoyl dithiocarbazate with iodine produces an unstable linear disulfide corresponding to the thiuram disulfides. This same product forms in solid potassium benzoyl thiocarbazate by air oxidation. Six previously unreported oxadiazolinethiones have been prepared by the usual alkaline cyclization.

Since its preparation and identification in 1904, potassium benzoyldithiocarbazate (I, R = C_6H_5)[1] has been used as an intermediate in a number of syntheses. Busch and Stark[1] prepared several esters (II, R = C_6H_5), while Hoggarth[2] showed that boiling an alcoholic solution of the salt caused cyclization to 2-mercapto-5-phenyl-1,3,4-oxadiazole (III, R = C_6H_5). He also showed that the latter could be converted to the methylthio derivative (V, R = C_6H_5,R′ = CH_3). By the use of analogs of potassium benzoyldithiocarbazate, Young and Wood[3] and Ainsworth[4] prepared a series of 5-substituted - 2 - mercapto - 1,3,4 - oxadiazoles. However, they pointed out that infrared absorption spectra show the presence of N—H and C=S bands, an observation which indicates that these substances exist as the thiones (IV) rather than the mercapto compounds (III). Further study with the esters (II)[3] and amides[5] of substituted dithiocarbazic acids showed that they could be cyclized by cold concentrated sulfuric acid to 1,3,4-thiadiazoles (VI) in contrast to the 1,3,4-oxadiazoles formed by cyclization of the potassium salts in alkaline solution.



Application of this procedure to substituted potassium dithiocarbazates has led to a number of 1,3,4-thiadiazoline-5-thiones (Table I).

Although 2-phenyl-1,3,4-thiadiazoline-5-thione (VII, R = C_6H_5)[6] and its 2-(4-pyridyl) analog

(1) M. Busch and M. Stark, *J. prakt. Chem.*, **93**, 49 (1916); H. Felin, *Inaugural Dissertation*, Erlangen University (1904).

(2) E. Hoggarth, *J. Chem. Soc.*, 4811 (1952).

(3) R. W. Young and K. H. Wood, *J. Am. Chem. Soc.*, **77**, 400 (1955).

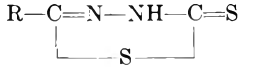
(4) C. Ainsworth, *J. Am. Chem. Soc.*, **78**, 4475 (1956).

(5) S. Yoshida and M. Asai, *J. Pharm. Soc. Japan*, **74**, 951 (1954); *Chem. Abstr.*, **49**, 10937 (1954).

(6) B. Holmberg, *Arkiv Kemi, Mineral. Geol.*, **17A**, 1 (1944); *Chem. Abstr.*, **39**, 3524 (1945).

TABLE I

1,3,4-THIADIAZOLINE-5-THIONES

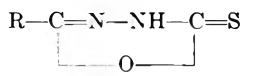


R=	Yield, %	M.P., °C.	Empirical Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
p-$CH_3OC_6H_4$	35	222–224	$C_9H_8N_2OS_2$	48.1	48.2	3.6	3.4	12.5	12.0	28.6	28.3
p-ClC_6H_4[a]	35	210–212	$C_8H_5N_2S_2Cl$	41.8	41.8	2.2	2.2	12.3	12.0	28.1	28.2
n-C_7H_{15}[b]	73	56–58	$C_9H_{16}N_2S_2$	50.2	49.9	7.0	7.1	13.1	12.8	29.7	29.7
2-Furoyl	17	221–223	$C_6H_4N_2OS_2$	39.1	39.1	2.2	2.1	15.3	15.0	—	—
3-Pyridyl[c]	30	219–221	$C_7H_5N_3S_2$	43.1	43.1	2.6	2.9	21.6	22.0	32.7	32.7

[a] % Cl Calcd./found 15.6/14.9. [b] Recrystallized from light petroleum. [c] Recrystallized from 95% ethanol.

TABLE II

1,3,4-OXADIAZOLINE-5-THIONES



R=	Yield, %	M.P., °C.	Empirical Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
m-$NO_2C_6H_4$[b]	36	132–134	$C_8H_5N_3O_3S$	43.0	43.9[c]	2.3	2.4	18.8	18.8	14.2	14.5
o-$CH_3OC_6H_4$[b]	35	223–226	$C_9H_8N_2O_2S$	51.9	52.4	3.9	4.3	13.4	13.8	—	—
o-$CH_3C_6H_4$[a]	37	190–191	$C_9H_8N_2OS$	56.2	56.1	4.2	4.3	14.6	14.4	16.7	16.8
m-$CH_3C_6H_4$[b]	20	158–160	$C_9H_8N_2OS$	56.2	56.0	4.2	4.3	14.6	14.3	16.7	16.8
o-HOC_6H_4[a]	20	212–213	$C_8H_6N_2O_2S$	49.5	49.3	3.1	2.9	14.4	14.0	16.5	16.6
p-HOC_6H_4[a]	64	252–254	$C_8H_6N_2O_2S$	49.5	49.3	3.1	3.2	14.4	14.7	16.5	16.5

Cyclization conditions [a] KOH in ethanol, [b] pyridine. [c] Several carbon-hydrogen analyses were run on this compound and all results were high.

(VII, R = 4-pyridyl)[7] have been reported, they were prepared by cyclization of potassium thiobenzoyl- and thioisonicotinoyl-dithiocarbazates (X, R = C_6H_5, 4-pyridyl), respectively, with potassium hydroxide in ethanol. The present method offers a distinct advantage, since X (R = C_6H_5) and its homologs are not easy to obtain. Pertinent data for five thiadiazolinethiones and six oxadiazolinethiones hitherto unreported are given in Tables I and II.[8]

A study of the action of sulfuric acid on potassium benzoyldithiocarbazate revealed that, in addition to the thiadiazolinethione, a second substance is formed. The amount of this substance increases at the expense of the thiadiazolinethione if the temperature exceeds 10°. It increases even more if the potassium benzoyldithiocarbazate is not freshly prepared. Apparently, this by-product is due, in part, to the oxidizing power of sulfuric acid and in part to air oxidation. Reference to Table III shows roughly how the yield of by-product increases under oxidizing conditions.

Further investigation of the by-product showed that it is the disulfide VIII (R = C_6H_5); this was established by oxidation of the thiadiazolinethione

TABLE III

ACID CYCLIZATION OF POTASSIUM BENZOYLDITHIOCARBAZATE

Age	Freshly Prepared		3 Months Old Sample	
Temperature	<10°	40–50°	10°	40–50°
Yield of thiadiazolinethione	67%	40%		—
Yield of by-product	—	13%		51%

(VII, R = C_6H_5) with iodine to a disulfide identical with VIII (R = C_6H_5). Because of the high yield of by-product obtained from aged potassium benzoyldithiocarbazate and because it did not seem reasonable that air oxidation would effect a cyclization, the aged product was investigated for a possible intermediate. Such an intermediate was obtained and it appears to be the non-cyclic disulfide, IX (R = C_6H_5). This same product can be prepared from fresh potassium benzoyldithiocarbazate by oxidation with iodine[9] and can be cyclized to the disulfide VIII (R = C_6H_5) with sulfuric acid. However, it has not been possible to obtain the non-cyclic product in analytically pure form. Attempts at purification resulted in further reaction with the formation of the oxadiazole and sulfur.

Despite the fact that the assumed intermediate could not be isolated in pure form, such a structure

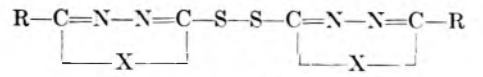
(7) H. B. König, W. Siefken, and H. A. Offe, *Ber.*, **87**, 825 (1954).

(8) These substances are described as the thiones because the infrared data are similar to that described by Ainsworth,[4] who has reported that a more detailed study of the infrared absorption of such compounds will be published by H. Boaz.

(9) P. Ch. Guha, *J. Am. Chem. Soc.*, **44**, 1503 (1922).

TABLE IV

DISULFIDES OF 1-OXA- AND THIA-3,4-DIAZOLES



R=	X	Yield, %	M.P., °C.	Empirical Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
C_6H_5	0	56	194–196	$C_{16}H_{10}N_4O_2S_2$	54.2	54.3	2.9	2.7	15.8	16.3	18.1	18.4
m-$CH_3C_6H_4$	0	40	120–121	$C_{18}H_{14}N_4O_2S_2$	56.5	56.9	3.7	4.0	14.6	14.9	16.7	16.4
C_6H_5	S	76	160–162	$C_{16}H_{10}N_4S_4$	49.7	49.3	2.6	2.6	14.5	14.4	33.2	33.5

is not new. The well-known thiuram disulfides (RNHCSSSSCNHR) are not stable compounds.[10] Furthermore, a similar, non-cyclic disulfide (IX, R = 4-pyridyl) has been reported recently,[7] but details of preparation or isolation are not disclosed.

The S—S— linkage could not be characterized by infrared spectroscopy. However, a polarographic study of potassium benzoyldithiocarbazate and the cyclic and non-cyclic disulfides yielded information[11] which, together with the chemical evidence, is consistent with the proposed structure (IX).

EXPERIMENTAL

Potassium 3-aroyl- or 3-acyl-dithiocarbazates (I) were prepared in good yield and quality by a known method.[1] If the salt was not to be used immediately, it was stored in a vacuum desiccator.

2-Substituted-1,3,4-thiadiazoline-5-thiones (VII). Approximately 0.1 mole of the potassium salt (I) was powdered and added in small portions, with vigorous stirring, to cold (0–2°), concentrated sulfuric acid (*d* 1.82) (5 ml. per g. of the salt). The temperature was not allowed to exceed 6–8°; the solid dissolves quite rapidly. Stirring was continued 3–5 min. after the addition had been completed.

The solution was poured upon ice (50 g. per g. of potassium salt). The yellowish solid that separated was collected on a filter, washed with water, pressed as dry as possible, and recrystallized (decolorized first with Norit) from 50% ethanol (Table I).

2-Substituted-1,3,4-oxadiazoline-5-thiones (III) were prepared by heating the potassium salts (I) in pyridine[2] or by boiling an alcoholic (95%) solution of the salt formed by addition of carbon disulfide to an alkaline solution of the hydrazide.[4] The latter was preferred because it did not involve isolation of the potassium salts and the yields were higher (Table II).

Bis(5-substituted-1,3,4-oxa(thia)-diazol-2-yl) disulfides (VIII *and* XI). The 2-substituted-1,3,4-oxa- or thiadiazoline-5-thione (0.01 to 0.05 mole) was dissolved in 20–35 ml. of 5% aqueous potassium hydroxide. A 1–2% aqueous solution of iodine containing 3% of potassium iodide was added in small portions, with stirring, at room temperature, until the abundant precipitate that formed turned slightly brown. The solid was collected and then recrystallized from ethanol. One disulfide (VIII, R = C_6H_5) was also prepared through acid treatment of IX (R = C_6H_5), following the same procedure indicated for VII (yield, 73%).

Analytical data for this disulfide and for two disulfides derived from oxadiazolinethiones are given in Table IV.

Bis(3-benzoyldithiocarbazoyl) disulfide (IX, R = C_6H_5). (*1*) A sample of 10 g. of potassium 3-benzoyldithiocarbazate was allowed to stand in an open bottle for 3 months. The sample was then stirred into cold water and the *p*H adjusted to 8 by addition of a few drops of hydrochloric acid. The undissolved solid (1.0 g., m.p. 210–212°) was not further purified.

Anal. Calcd. for $C_{16}H_{14}O_2N_4S_4$: C, 45.4; H, 3.4; N, 13.3; S, 30.3. Found: C, 42.7; H, 2.5; N, 12.8; S, 30.8.

(*2*) Fresh potassium 3-benzoyldithiocarbazate (5 g.) was treated with a 1% iodine solution (as described for VIII and XI). The yellowish solid (2 g.) obtained had m.p. 210–212° and showed no depression in melting point on admixture with the product from (*1*).

Infrared spectra[12] *of* I *and* IX. The infrared absorption spectra were obtained on a Baird double-beam spectrophotometer, Model AB-1 (with NaCl prism). The absorption peaks due to —NH at 3μ and to —CONHR at 6.1 and 6.5–6.6μ were present, as expected in both the potassium salt (I) and the disulfide (IX). The —NHCS— absorption at 6.8μ in IX is a more normal position than the band at 7.2μ in I, for which this group is presumably responsible. This shift may be attributed to the polar potassium salt. The S—S— linkage could not be characterized.

ROCHESTER 4, N. Y.

(10) J. v. Braun, *Ber.*, **35**, 3368–3388 (1902).

(11) Polarograms of these materials were run by E. P. Przybylowicz, of these Laboratories. The sample was dissolved in a 1:1 mixture of acetone and methanol and diluted to twice its volume with an acetate buffer of *p*H = 5. The potassium salt (I) produced a well-defined anodic wave which can be assigned to the dithiocarbazate grouping. It also gave a small cathodic wave which could represent the presence of a small amount of disulfide. The product assigned the structure IX and the cyclic disulfide (VIII) gave no anodic waves, but each produced two well-defined cathodic waves. The polarograms of these two samples were virtually identical. From these data it is concluded that products VIII and IX contain similar reducible groups which are not present in I. However, since IX is derived from I by oxidation, it can be concluded that the cathodic waves observed in it and VIII are due to the disulfide grouping.

(12) We are indebted to D. W. Stewart, of these Laboratories, for the infrared data.

[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY, UNIVERSITY OF TENNESSEE AND TULANE UNIVERSITY]

Bis(3-thianaphthenoyl)furoxan

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The action of nitric acid on 3-acetylthianaphthene in acetic acid solvent leads to a product shown to be bis(3-thianaphthenoyl)furoxan (I). Evidence for this structure is (*1*) similarity of infrared and ultraviolet spectra to the spectra of known furoxans, (*2*) accelerating effect of nitrite ion on the rate of formation of the product and (*3*) cleavage of the product with phenylhydrazine to yield 1-(3-thianaphthenoyl)-2-phenylhydrazine (II) and 3-(β-phenylhydrazino)-4-nitroso-5-(3-thianaphthenyl)isoxazole (III). 2-Acetylthianaphthene and 3-acetyl-2-methylthianaphthene were also converted to the corresponding furoxans.

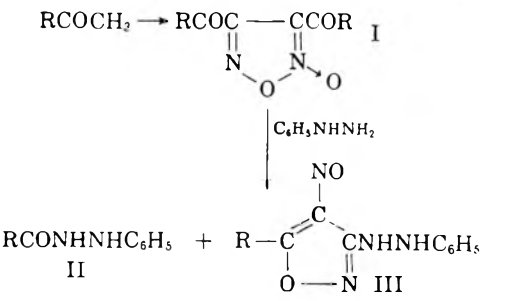
As a part of a continuing program of study of the fundamental chemistry of the thianaphthene ring, we carried out the "nitration" of 3-acetylthianaphthene with concentrated nitric acid in glacial acetic acid solvent at the boiling point of the mixture. There was formed in good yield a light yellow crystalline solid, m.p. 196–197°, which was obviously not a nitro derivative of the 3-acetylthianaphthene. Later Buu-Hoï and Hoan[1] reported the formation of 2-nitro-3-acetylthianaphthene from nitration of 3-acetylthianaphthene with acetic anhydride, fuming nitric acid and glacial acetic acid at 0–5°.

Among several structural possibilities, corresponding to the empirical formula of $C_{10}H_5NO_2S$ for the new compound, was bis(3-thianaphthenoyl)-furoxan (I), since diaroylfuroxans have been shown to be formed from methyl aryl ketones[2] and nitric acid. The publication of a study of the infrared spectra of furoxans,[3] including some diarylfuroxans, provided good evidence in favor of a furoxan structure for our compound, since bands appeared in its infrared spectrum corresponding to seven bands designated[3] as characteristic of furoxans. These are indicated in Table I.

Ultraviolet spectra also furnished some evidence for the furoxan structure. Dibenzoylfuroxan shows a single maximum at 267 mμ in ethanol. The maximum for acetophenone is 242 mμ[4] indicating a bathochromic shift of 25 mμ in going from the ketone to the furoxan. A similar shift of 25 mμ is observed in a comparison of 2-acetylfuran (λ_{max}, 270 mμ) and the corresponding furoxan (λ_{max}, 295 mμ).[5] The spectrum of 3-acetylthianaphthene shows a maximum at 304 mμ. Bis(3-thianaphthenoyl)furoxan exhibits a maximum at 330 mμ, representing a bathochromic shift of 26 mμ. The ultraviolet absorption maximum for furoxans varies, as would be expected, with the nature of the groups attached. J. H. Boyer and co-workers[6] report a characteristic furoxan absorption in the range 255–285 mμ, but none of the compounds examined contained a carbonyl group conjugated to the furoxan ring. Dibenzoylfuroxan absorbs in this range but it is expected that the more highly conjugated thianaphthene type would absorb at a longer wave length.

In order to obtain evidence that the action of nitric acid on 3-acetylthianaphthene did not involve the 2-position, we carried out the reaction of 2-methyl-3-acetylthianaphthene with nitric acid. The product of the reaction showed analytical values and infrared absorption bands (Table I) characteristic of the furoxan structure. 2-Acetylthianaphthene was also converted to the corresponding furoxan.

In accordance with observations of other workers[2,7] that nitrite ion accelerates the rate of formation of diaroylfuroxans from methyl aryl ketones, we observed a marked accelerating effect on the reaction of 3-acetylthianaphthene.



Quist[8] has reported the formation of two products from the reaction of dibenzoylfuroxan and phenylhydrazine. These are 1-benzoyl-2-phenylhydrazine and 3-(β-phenylhydrazino)-4-nitroso-5-phenylisoxazole. Bis(3-thianaphthenoyl)furoxan underwent

(1) Ng. Ph. Buu-Hoï and Ng. Hoan, *J. Chem. Soc.*, 251 (1951).

(2) See H. R. Snyder and N. E. Boyer, *J. Am. Chem. Soc.*, **77**, 4233 (1955) for some leading references.

(3) N. E. Boyer, G. M. Czerniak, H. S. Gutowsky, and H. R. Snyder, *J. Am. Chem. Soc.*, **77**, 4238 (1955).

(4) R. B. Turner and D. M. Voitle, *J. Am. Chem. Soc.*, **73**, 1403 (1951).

(5) K. Hayes and C. O'Keefe, *J. Org. Chem.*, **19**, 1897 (1954).

(6) J. H. Boyer, U. Toggweiler, and G. A. Stoner, *J. Am. Chem. Soc.*, **79**, 1748 (1957).

(7) G. Ponzio, *Gazz. chim. ital.*, **56**, 490 (1926); *Chem. Abstr.*, **21**, 239 (1927).

(8) W. Quist, *Acta Acad. Aboensis, Math. et Phys.*, **5**, 16 (1928); *Chem. Zentr.*, 1929 *I*, 892.

TABLE I

INFRARED DATA

Characteristic[a] Bands (Ranges in μ)	Dibenzoylfuroxan[a]	Bis(3-thianaphthenoyl)furoxan	Bis(2-methyl-3-thianaphthenoyl)-furoxan
6.15–6.25	6.23 s	6.22 s	6.20 s
6.78–7.09 (doublet)	6.80 m, 6.90 s	6.83 s, 7.04 s	6.83 m, 7.00 s
7.35–7.69	7.54 s	7.26 m	7.46 m
8.40–8.70	8.51 m	8.35 s	8.42 m
9.71–10.00	9.76 w	9.63 s	9.64 w
10.53–11.11	10.91 s	10.56 w	11.05 w
11.24–11.90	11.20 s	11.90 m	11.70 w

[a] s-strong, m-medium, w-weak.

a similar reaction to give the corresponding products II and III.

All of these data indicated that the product from action of nitric acid on 3-acetylthianaphthene was bis(3-thianaphthenoyl)furoxan (I, R = 3-thianaphthenyl).

We have tried on several occasions to repeat the work of Buu-Hoï and Hoan[1] on the formation of 2-nitro-3-acetylthianaphthene by nitration of 3-acetylthianaphthene, but have been unable to obtain a product with the properties they described. We have also carried out the nitration of 3-thianaphthaldehyde in accordance with their directions, and have been unable to isolate the reported 2-nitro-3-thianaphthaldehyde.

EXPERIMENTAL[9]

3-Acetylthianaphthene. Most of the 3-acetylthianaphthene used was supplied by The Texas Co. Some was synthesized by acylation of thianaphthene by the method of Komppa,[10] but a better laboratory procedure in our hands was the reaction of dimethylcadmium and 3-thianaphthenoyl chloride.[11] This latter method allowed formation of 3-acetylthianaphthene in 64% yield.

Bis(3-thianaphthenoyl)furoxan. Sixteen grams (0.091 mole) of 3-acetylthianaphthene was dissolved in a solution of 32 ml. of concentrated nitric acid and 80 ml. of glacial acetic acid, and the resulting solution was placed in a 500-ml. round-bottomed flask. The flask was closed and allowed to stand at room temperature overnight. During this period, a yellow crystalline material precipitated from the solution and nitrogen dioxide was evolved. The yellow material was collected on a filter, washed with glacial acetic acid, and after drying weighed 11.4 g. (62%). The crude product melted at 191–193°. The material was best crystallized from a solution composed of water, methyl alcohol, and tetrahydrofuran. The white crystals thus obtained after drying weighed 8.3 g. and melted at 196–197° (λ_{max} 330 mμ; log ϵ, 4.06). The significant infrared absorption bands of the product are recorded in Table I.

Anal. Calcd. for $C_{20}H_{10}N_2O_4S_2$: C, 59.1; H, 2.47; N, 6.89; S, 15.8. Found: C, 59.23, 59.22; H, 2.64, 2.50; N, 6.96, 6.93; S, 15.83, 15.59.

The reaction of 3-acetylthianaphthene with concentrated nitric acid is greatly accelerated by the addition of a small quantity of sodium nitrite. The observation was based on the time required for the first trace of precipitate to form. In the case of the untreated reaction, the time required for the initial precipitation was 8 hr. By the addition of a trace of sodium nitrite, this period decreased to only 1 hr.

2-Acetylthianaphthene. This compound has been reported by Farrar and Levine[12] and Martznoff.[13] It was best prepared (54% yield) in this work by the action of anhydrous lithium acetate on 2-thianaphthenyllithium.[14] The organolithium compound was prepared by metalation of thianaphthene by *n*-butyllithium.[15]

Bis(2-thianaphthenoyl)furoxan. A solution of 6.0 g. (0.034 mole) of 2-acetylthianaphthene and 24 ml. of concentrated nitric acid in 70 ml. of glacial acetic acid was placed in a tightly stoppered flask and allowed to stand for 48 hr. The pressure was released and the precipitated yellow solid (4.55 g.) was removed by filtration. The product melted at 169–174°. Recrystallization raised the m.p. to 176–179° and a small sample recrystallized for analysis melted at 179–180°.

Anal. Calcd. for $C_{20}H_{10}N_2O_4S_2$: C, 59.1; H, 2.47; N, 6.89. Found: C, 58.8, 58.5; H, 2.44, 2.56; N, 6.71, 6.99.

The bis(2-thianaphthenoyl)furoxan showed an infrared spectrum similar to the 3-isomer up to about 7.5 μ and exhibited the "characteristic" aroyl furoxan bands (Table I) above this range.

3-Acetyl-2-methylthianaphthene was prepared by acetylation of 2-methylthianaphthene[15] by a procedure apparently better than that reported by Gaertner.[16] Nineteen grams (0.13 mole) of 2-methylthianaphthene was mixed with 12.2 g. (0.12 mole) of acetic anhydride in a 250-ml. flask equipped with a mechanical stirrer and a reflux condenser. The mixture was heated to facilitate solution and then 2.5 g. of anhydrous stannic chloride was added. An exothermic reaction occurred and this was followed by external heating for 1 hr. at a temperature just below the boiling point of the mixture. The reaction mixture was allowed to cool to room temperature and poured into 200 ml. of an ice-water slurry. When the hydrolysis mixture had warmed to room temperature, it was extracted twice with 100-ml. portions of ether. The ethereal extracts were combined and washed with 100 ml. of water and dried over anhydrous sodium carbonate. After removal of the solvent, the residue was distilled *in vacuo* to yield 8.8 g. (39%) of 3-acetyl-2-methylthianaphthene, b.p. 184–188°/23 mm. Recrystallization from hexane yielded 6.5 g. of tan crystals which melted at 67–69°. Gaertner[16] has reported the melting point of 3-acetyl-2-methylthianaphthene to be 69–70°.

(9) Microanalyses are by Galbraith Microanalytical Laboratory, Knoxville, Tenn., and Weiler and Strauss, Oxford, England. All melting and boiling points are uncorrected.

(10) G. Komppa, *J. prakt. Chem.*, **122**, 319 (1929).

(11) D. A. Shirley, *Org. Reactions*, **VIII**, Chapter 2 (1954).

(12) M. W. Farrar and R. Levine, *J. Am. Chem. Soc.*, **72**, 4433 (1950).

(13) M. Martznoff, *Compt. rend.*, **234**, 736 (1952).

(14) H. Gilman and P. R. Van Ess, *J. Am. Chem. Soc.* **55**, 1258 (1933).

(15) D. A. Shirley and M. D. Cameron, *J. Am. Chem. Soc.*, **74**, 664 (1952).

(16) R. Gaertner, *J. Am. Chem. Soc.*, **74**, 766 (1952).

Bis(2-methyl-3-thianaphthenoyl)furoxan. Two grams (0.010 mole) of 3-acetyl-2-methylthianaphthene was dissolved in a solution of 4 ml. of concentrated nitric acid and 15 ml. of glacial acetic acid. This solution was placed in a 50-ml. Erlenmeyer flask and the flask was stoppered. After only 3 hr. a yellow solid began to precipitate. At the end of 6 hr. the yellow material was collected on a filter. After air-drying the yellow solid weighed 1.3 g. and melted at 162–164°. Recrystallization of the material from a mixture of water, methanol, and tetrahydrofuran yielded yellow crystals which melted at 166–167°. (λ_{max} 336 mμ; log ϵ, 4.01). The characteristic infrared bands are recorded in Table I.

Anal. Calcd. for $C_{11}H_7NO_2S$: C, 60.82; H, 3.25; N, 6.44. Found: C, 60.80; H, 3.22; N, 6.36.

Reaction of bis(3-thianaphthenoyl)furoxan with phenylhydrazine. One gram (0.0025 mole) of the furoxan was suspended in 5 ml. of phenylhydrazine in a small flask and heated on a steam bath until an exothermic reaction began. This was noted by the evolution of a gas. Immediately the flask was removed from the source of heat and was allowed to cool slowly to room temperature. The reaction mixture was then poured into a large volume of water. After decanting the water layer, the residue was fractionally crystallized from 95% ethyl alcohol to yield two fractions, 0.20 g. which melted at 233.5–235° and 0.50 g. which melted at 192–193.5°.

The material melting at 233.5–235° was yellow and appears to be 3-(β-phenylhydrazine)-nitroso-(3-thianaphthenyl)isoxazole (III) which is analogous to the product obtained by Quist[8] from the reaction of dibenzoylfuroxan with phenylhydrazine.

Anal. Calcd. for $C_{17}H_{12}N_4O_2S$: C, 60.71; H, 3.60; N, 16.66; S, 9.52. Found: C, 60.72; H, 3.38; N, 16.2; S, 9.10.

The material melting at 192–193.5° was white and appears to be 1-thianaphthenoyl-2-phenylhydrazine which is analogous to a second product Quist[8] isolated from the reaction of dibenzoylfuroxan with phenylhydrazine.

Anal. Calcd. for $C_{15}H_{12}N_2OS$: C, 67.13; H, 4.51; N, 10.44. Found: C, 67.52; H, 4.59; N, 11.00, 10.80.

Acknowledgment. The authors would like to acknowledge the financial support of the Eli Lilly Co. and the National Science Foundation. The Texas Co. generously furnished a supply of 3-acetylthianaphthene. We should like to acknowledge helpful discussions with Professors J. H. Boyer and C. A. MacKenzie of Tulane University.

KNOXVILLE, TENN.

[CONTRIBUTION FROM THE RESEARCH STATION, THE BRITISH PETROLEUM COMPANY LIMITED]

Preparation and Physical Properties of Sulfur Compounds Related to Petroleum. IX. 7-Thiabicyclo[2.2.1]heptane and 6-Thiabicyclo[3.1.1]heptane

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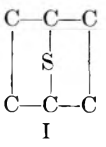
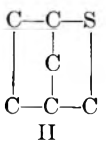
7-Thiabicyclo[2.2.1]heptane and 6-thiabicyclo[3.1.1]heptane have been synthesized and their physical properties recorded.

The presence of thiabicyclo-octanes and -nonanes in the tar oil recovered from the acid used in refining Agha Jari kerosine[1,2] suggested that thiabicycloheptanes might also be present. Since no compounds have been identified in straight-run distillates with rings containing fewer than five atoms the only thiabicycloheptanes considered were I and II and the synthesis of these compounds was undertaken to obtain their physical properties prior to examining the tar oil for their presence. This paper describes the preparation of I and its isomer, 6-thiabicyclo[3.1.1]heptane (VII), obtained in the course of the synthesis of I.



I



II

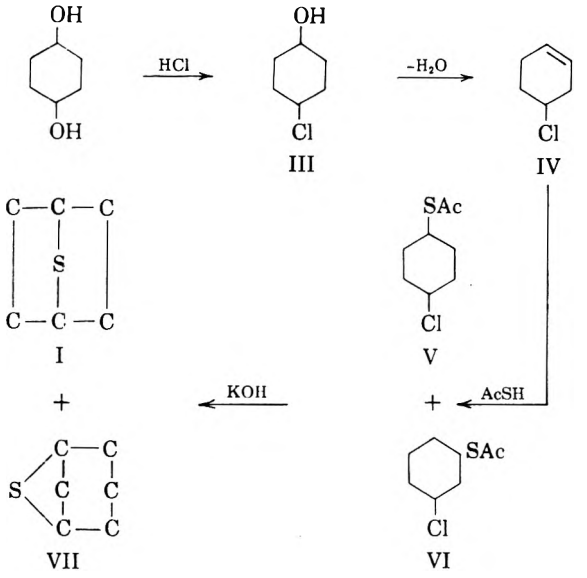
One obvious route for the synthesis of I, involving the addition of sulfur dioxide to 1,3-cyclohexadiene followed by hydrogenation of the sulfone and reduction of the product with lithium aluminum hydride (*cf.* 8-thiabicyclo[3.2.1]octane[3]), was found to be impractical as the initial addition product proved to be entirely polymeric. An attempt to obtain the sulfide by reaction of sodium sulfide with the ditosylate of cyclohexane-1,4-diol was also unsuccessful. The method finally used was based upon the hydrolysis and concomitant cyclization of the chlorocyclohexyl thioacetate V, prepared from 4-chlorocyclohexanol (III) as shown on page 1027.

Since the preparation entailed the addition of thioacetic acid to 4-chlorocyclohexene (IV), besides the required 4-chlorothioacetate the isomeric 3-chlorothioacetate was also produced which resulted in 6-thiabicyclo[3.1.1]heptane being formed as by-product. Separation of the two thiabicycloheptanes was, however, satisfactorily accomplished by

(1) S. F. Birch, T. V. Cullum, R. A. Dean, and R. L. Denyer, *Ind. Eng. Chem.*, **47**, 240 (1955).

(2) S. F. Birch, T. V. Cullum, and R. A. Dean. Paper presented at a Symposium on Polycyclic Hydrocarbons, Divisions of Petroleum Chemistry and Organic Chemistry, 130th Meeting of the American Chemical Society, Atlantic City, N. J., September 1956.

(3) S. F. Birch, R. A. Dean, N. J. Hunter, and E. V. Whitehead, Part VII of this series to be published in the Journal.



fractional distillation in the presence of isopropylcyclohexane. 2-Naphthalenesulfonic acid was chosen for the dehydration of III since the work of Vogel,[4] Bousset[5] and Kohler *et al.*[6] indicated that this would give IV uncontaminated with isomeric chlorocyclohexenes. The reaction of thioacetic acid with IV was very erratic. On occasions only some 25% reaction occurred even when radical-forming compounds were present and/or the mixture was irradiated with light from tungsten-filament or ultraviolet lamps. On other occasions the mixture reacted spontaneously when the reactants were mixed and a theoretical yield was obtained. This spontaneous reaction frequently took place in the receiver when unreacted materials were recovered by distillation from the product of an incomplete reaction. No explanation of the unpredictable course of this reaction has been obtained, but the most likely theory appears to be that an inhibitor can be formed by a side-reaction and that this, if formed in sufficient quantity, almost entirely stops the reaction. However, despite this, the final yield of thioacetates was 86%. Hydrolysis of the product gave a mixture of the two thiabicycloheptanes (I and VII), cyclohexenethiols, and some polymeric material. Since a Walden inversion would be expected to occur at the cyclization stage[3] and the sulfides exist only in the *cis* form (*cf.* the thiabicyclo [3.2.1] octanes[3]), it is presumed that the sulfides were formed from the *trans*-thioacetates and the by-products were mainly derived from the *cis*-thioacetates.

Separation of the mixture of sulfides was attempted by crystallization. This was unsuccessful since both were solids and were present in roughly equal amounts. Fractional distillation was rejected because of the practical difficulties associated with the distillation of solids with high melting points. Distillation in the presence of isopropylcyclohexane, however, proved completely successful in separating the two sulfides since the lower boiling component formed an azeotrope (this was predicted from previous experience[7]) while the higher boiling did not and remained in the residue. The azeotrope was not obtained free from the entrainer since the boiling points were very close but complete separation was obtained by continuing the distillation until a negligible amount of sulfide was present in the distillate. The sulfides were separated from the hydrocarbon by adsorption on silica gel and finally purified by crystallization from acetic acid. The properties of the two thiabicycloheptanes are recorded in Table I; the infrared spectra were obtained in the range 2–15μ.[8]

TABLE I

PHYSICAL PROPERTIES OF THE SULFIDES

Sulfide	M.P., °C.	B.P. °C.	B.P. Mm.	n_D^{20}
7-Thiabicyclo[2.2.1]-heptane	127.5–128.5	164	765	1.517[c]
6-Thiabicyclo[3.1.1]-heptane	93.5–95.5	175	775	1.519[d]

[a] By proportion from the values of solutions in di-*n*-butyl sulfide.

At this stage it was not known with certainty which of the two isomers had the structure of I although some indication had been obtained from the relative stabilities of the mercuric salt complexes. Attempts to separate the sulfides by crystallization and regeneration of the mercuric chloride derivatives of the mixture gave only an intractable plastic solid from which a small amount of mercaptan-containing oil was obtained on regeneration; on the other hand, extraction of a pentane solution of the mixed sulfides with aqueous mercuric acetate solution followed by regeneration of the extract gave one sulfide only, identical with the lower boiling compound. Since the residual aqueous liquors contained a mercapto alcohol it was assumed that the higher boiling compound was the 6-thiabicyclo-[3.1.1]heptane and that this formed unstable mercuric salt derivatives owing to the sulfur atom being in a 4-membered ring (*cf.* thiacyclobutane[9]). The correctness of this assumption was shown when a small amount of a mixture of 6-thiabicyclo-[3.1.1]heptane and 7-thiabicyclo [4.1.0] heptane (X) (cyclohexene sulfide[10]) was prepared by the

(4) A. I. Vogel, *J. Chem. Soc.*, 1323 (1938).
(5) A. Bousset, *Bull. soc. chim.*, **6**, 983 (1939).
(6) E. P. Kohler, M. Tishler, H. Potter, and H. T. Thompson, *J. Am. Chem. Soc.*, **61**, 1057 (1939).
(7) D. H. Desty and F. A. Fidler, *Ind. Eng. Chem.*, **43**, 905 (1951).
(8) To be submitted to the API Research Project 44 for inclusion in their catalog of spectral data.
(9) E. Grischkevitsch-Trochimovski, *J. Russ. Phys. Chem. Soc.*, **47**, 880 (1916).
(10) E. E. van Tamelen, *J. Am. Chem. Soc.*, **73**, 3444 (1951).

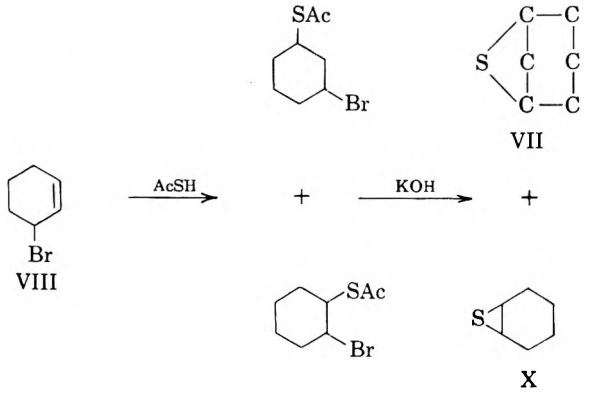
TABLE II

MELTING POINTS AND ANALYSES OF THE DERIVATIVES OF THE SULFIDES

Compound	Formula of Derivative	M.P., °C. (Corrected)	Analyses					
			Calcd.			Found		
			C	H	S	C	H	S
7-Thiabicyclo[2.2.1]-heptane	$C_6H_{10}Cl_2HgS$	186.5–187.5 dec.	18.7	2.6	8.3	18.6	2.7	8.4
	$C_6H_{10}O_2S$	253–254[a]	49.3	6.9	21.9	49.4	7.0	22.2
	$C_7H_{13}IS$	138–139 dec.[a]	32.8	5.2	12.5	33.0	5.1	12.5
6-Thiabicyclo[3.1.1]-heptane	$C_6H_{10}O_2S$	171.5–172.5	49.3	6.9	21.9	49.5	6.7	21.8

[a] Sealed tube.

method shown below. The infrared spectrum of the mixture, which was semi-solid at room temperature, was obtained and comparison of this spectrum with those of the pure sulfides showed that the higher boiling sulfide was present to the extent of at least 50% and that the lower boiling one could not be detected. 6-Thiabicyclo[3.1.1]heptane was ob-



served to decompose to some extent at its atmospheric boiling point with the formation of a white solid insoluble in the usual solvents. Further evidence of the instability of this sulfide was obtained when it was found that a sample which had been degassed and sealed under vacuum was partly converted into non-volatile material under the influence of daylight. The original sulfide gave a positive result in the acrylonitrile test for free radicals,[11] indicating that in the absence of oxygen, which presumably normally acts as an inhibitor, 6-thiabicyclo[3.1.1]heptane undergoes a light-initiated radical polymerization. Thiacyclobutane itself has been found to behave similarly in the absence of oxygen[12] but rough comparative tests with this compound showed that, although it was more effective in polymerizing acrylonitrile, it was not nearly so susceptible to self-polymerization as VII. 6-Thiabicyclo[3.1.1]heptane is readily decomposed by concentrated sulfuric acid, polymeric material again being formed (*cf.* thiacyclobutane[13]).

7-Thiabicyclo[2.2.1]heptane was characterized by means of the usual derivatives. No further attempt was made to prepare the mercuric chloride complex of 6-thiabicyclo[3.1.1]heptane; with methyl iodide the sulfide gave only an oil but the sulfone was obtained by the usual method. The melting points and analyses of the derivatives are recorded in Table II.

7-Thiabicyclo[2.2.1]heptane has not so far been detected in those fractions of the tar oil in which, from its boiling point, it might be expected to occur. It is interesting to note that Rossini and his co-workers have recently shown[14] that a hydrocarbon having this ring structure is probably present in the representative petroleum of A.P.I. Research Project 6.

EXPERIMENTAL

All melting points are corrected. All sublimations were carried out under reduced pressure. Microanalyses are by Dr. Ing. A. Schoeller, Kronach/Oberfranken, Bambergerstrasse 20, Germany.

4-Chlorocyclohexanol (III) (b.p. 96–106°/10 mm., n_D^{20} 1.4947) was obtained in average yield of 60% from 1,4-cyclohexanediol.[15]

4-Chlorocyclohexene (IV). 4-Chlorocyclohexanol (108 g.) and 2-naphthalenesulfonic acid (5 g.) were heated in an oil-bath at 200–240° and the distillate was taken off through a short, glass-packed column. The organic layer was dried over calcium chloride and the fraction, b.p. 88–93°/130 mm., n_D^{20} 1.4822 (48 g., 51%) was taken as 4-chlorocyclohexene, leaving a residue of polymeric material.

Chlorocyclohexyl thioacetates (V *and* VI). (*a*) Portions (*ca.* 0.2 mole) of 4-chlorocyclohexene were mixed with thioacetic acid (*ca.* 0.3 mole, b.p. 86–87.5°/763 mm., n_D^{20} 1.4646–1.4648) and the mixtures were allowed to stand for various periods (2–20 hr.), under various conditions of temperature (20–90°) and illumination (daylight, 100-watt tungsten-filament lamp, ultraviolet), and in one instance a trace of azobisisobutyronitrile was added as a radical source. Reaction was not vigorous under any of these conditions and only moderate yields (20–45%) of addition products (b.p. 106–112°/3 mm.) were obtained. Complementary amounts of unreacted materials were recovered as forerunnings, and these usually reacted spontaneously in the receiver giving

(11) J. H. Baxendale, M. G. Evans, and G. S. Park, *Trans. Faraday Soc.*, 42, 155 (1946); *cf.* S. F. Birch, T. V. Cullum, and R. A. Dean, *J. Inst. Pet.*, 39, 206 (1953).

(12) W. E. Haines, G. L. Cook, and J. S. Ball, *J. Am. Chem. Soc.*, 78, 5213 (1956).

(13) D. S. Tarbell and D. P. Harnish, *Chem. Revs.*, 49, 1 (1951).

(14) B. J. Mair, P. E. Eberly, Kun Li, and F. D. Rossini. Paper presented at the Symposium quoted in Ref. 2.

(15) L. N. Owen and P. A. Robins, *J. Chem. Soc.*, 320 (1949).

further quantities (20–70%) of the required addition products, but sometimes the reaction went to completion only after a second recovery of unreacted materials. (*b*) 4-Chlorocyclohexene (0.3 mole) was distilled under nitrogen (50 mm.) into an ice cooled flask and thioacetic acid (0.45 mole) was distilled under nitrogen (50 mm.) into the same receiver. On removal of the ice, vigorous reaction occurred spontaneously and it became necessary to cool the mixture to moderate the reaction. The mixture was allowed to stand half an hour after the reaction appeared to have ceased and was then distilled giving 55 g. (98%) of thioacetate. In a second preparation carried out under these conditions, reaction was not vigorous and only 60% of addition product was obtained initially. The recovered starting materials reacted spontaneously to give a further quantity of thioacetate: total yield 91%.

Redistillation of the combined products from (*a*) and (*b*) gave an 86% yield of the thioacetates, b.p. 98–102°/2 mm., n_D^{20} 1.5195.

Preparation of 7-thiabicyclo[2.2.1]heptane (I) *and 6-thiabicyclo[3.1.1]heptane* (VII). The thioacetate mixture (274 g.) was added dropwise during 30 min. to refluxing aqueous ethanolic caustic potash (KOH, 770 g.; EtOH, 1925 ml.; H_2O, 1925 ml.), refluxing then being continued for 2 hr. The reaction mixture was distilled until thiol began to come over in appreciable quantities and the distillate was then diluted with water and extracted with *n*-pentane. The extracts were shaken with iodine and 10% aqueous caustic potash until free from thiol, and sublimation of the solid left on evaporation, gave a mixture of 7-thiabicyclo[2.1.1]-heptane and 6-thiabicyclo[3.1.1]heptane (66 g., 41%) melting at 105–108°. Infrared spectroscopy showed the composition to be 42% and 58%, respectively.

Further distillation of the aqueous residues from the thioacetate hydrolyzate and extraction of the distillate with *n*-pentane gave 42 g. of material b.p. 30°/27 mm.–150°/3 mm. The alkali soluble portion (20 g.) of the fraction (25 g.) b.p. 62–64°/27 mm., had b.p. 78–79°/47 mm., n_D^{20} 1.5177. This was probably a mixture of cyclohexene thiols.

Anal. Calcd. for $C_6H_{10}S$: C, 63.1; H, 8.8; S, 28.1. Found: C, 63.0; H, 8.7; S, 27.8.

2,4-Dinitrochlorobenzene derivative, m.p. 106–107° from ethanol.

Anal. Calcd. for $C_{12}H_{12}N_2O_4S$: C, 51.4; H, 4.2; S, 11.4; N, 10.1. Found: C, 51.9; H, 4.5; S, 11.3; N, 10.0.

Separation of 7-thiabicyclo[2.1.1]heptane (I) *and 6-thiabicyclo[3.1.1]heptane* (VII) *by azeotropic distillation.* A quantity (15.8 g.) of the mixture of the sulfides (m.p. 105–108°) was dissolved in isopropylcyclohexane (600 ml., b.p. 83°/81 mm., n_D^{20} 1.4909; purified by percolation over silica gel) and this mixture was distilled at reduced pressure (81 mm.) through a 40-plate, glass-packed column until several consecutive fractions of n_D^{20} 1.4911, b.p. 82.8°/81 mm. were obtained (initial fractions had n_D^{20} 1.4946≡*ca.* 5% sulfide and b.p. 79.5°/81 mm.). The distillate fractions were combined (total 400 ml.) and percolated over silica gel (170 g., 28–200 mesh), using *n*-pentane (100 ml.) to displace the isopropylcyclohexane, and ethanol to elute the sulfide. The 7-thiabicyclo[2.2.1]heptane was separated in the usual way and sublimed to give 5.5 g. (83% recovery based on that present in the original mixture) of m.p. 123–126°. 6-Thiabicyclo[3.1.1]heptane (7.0 g., 76% recovery), separated in the same manner from the distillation residue, was crystallized from glacial acetic acid to a constant melting point of 93.5–95.5°.

Anal. Calcd. for $C_6H_{10}S$: C, 63.1; H, 8.8; S, 28.1. Found: C, 62.7; H, 9.1; S, 28.2.

Isolation of 7-thiabicyclo[2.1.1]heptane (I) *by mercuric acetate treatment.* A solution of 0.4 g. of the mixture of sulfides in *n*-pentane (5 ml.) was extracted with four 5-ml. portions of aqueous mercuric acetate [$Hg(OAc)_2$, 500 g.; H_2O, 1500 ml.; HOAc, 25 ml.]. The combined extracts were added to refluxing aqueous sodium sulfide [30 ml. of 1:1 (w/w)/-$Na_2S{\cdot}9H_2O$:H_2O] and the regenerated sulfide was sublimed to give a solid (*ca.* 0.1 g.) melting at 126–127°. Continuous ether extraction of the aqueous sodium sulfide liquors for 16 hr. resulted in isolation of *ca.* 0.1 g. of an unpleasant smelling mobile oil (n_D^{20} 1.5256) the infrared spectrum of which indicated it to be a mercapto alcohol.

Anal. Calcd. for $C_5H_{12}OS$: C, 54.5; H, 9.2; S, 24.2. Found: C, 54.8; H, 8.8; S, 23.8.

A further quantity (11.4 g.) of 7-thiabicyclo[2.2.1]heptane was obtained by this treatment and purified to a constant melting point of 127.5–128.5° by crystallization of its mercuric chloride complex (31 g.) followed by crystallization of the regenerated sulfide from glacial acetic acid.

Anal. Calcd. for $C_6H_{10}S$: C, 63.1; H, 8.8; S, 28.1. Found: C, 63.3; H, 8.9; S, 27.8.

Preparation of VII *and 7-thiabicyclo[4.1.0]heptane* (X). 3-Bromocyclohexene (14.5 g., b.p. 75–79°/30 mm.), prepared[16] in 51% yield from cyclohexene and *N*-bromosuccinimide, was distilled in a nitrogen atmosphere under reduced pressure into an ice cooled flask containing thioacetic acid (8.5 g.) similarly distilled under nitrogen. Since there was no apparent reaction on allowing the mixture to warm to room temperature it was allowed to stand for several days, during which time there was slow evolution of hydrogen bromide, and it was then distilled under reduced pressure. The fraction (4.0 g., 19%) boiling over the range 72–100°/0.5 mm. (mostly at about 90°/0.5 mm.), n_D^{20} 1.539–1.543, was refluxed for 1 hr. with aqueous ethanolic caustic potash (KOH, 20 g.; EtOH, 50 ml.; H_2O, 50 ml.). Distillation of the material obtained by *n*-pentane extraction of the aqueous ethanolic distillate from the hydrolyzate gave 0.12 g. (6%) of an oil which gradually solidified.

Properties of 6-thiabicyclo[3.1.1]heptane. A sample of 6-thiabicyclo[3.1.1]heptane which had been degassed and sealed under vacuum in a Pyrex U-tube was allowed to stand in diffuse daylight for several hours. One limb of the tube was then cooled in liquid nitrogen and, while most of the solid readily sublimed into this limb, a portion was found to be comparatively nonvolatile. The limb containing the 6-thiabicyclo[3.1.1]heptane thus freshly sublimed was sealed off, while still maintaining the vacuum, and this was exposed to strong sunlight for 1 hr. At the end of this period the sulfide had been converted almost entirely to an amorphous, opaque, nonvolatile solid. This on further standing in the dark, was transformed to a translucent material which appeared to be semisolid. A sample of thiacyclobutane similarly degassed and sealed was exposed to strong sunlight for several hours and to diffuse daylight for several days, but even then the sample readily distilled to a liquid nitrogen-cooled portion of the tube, leaving only a small nonvolatile oily residue.

Both 6-thiabicyclo[3.1.1]heptane and thiacyclobutane gave positive results in the acrylonitrile test[17] for radial formation. After a few hours in strong sunlight, a considerable amount of white solid polymer had formed in the tube containing the nitrile to which 6-thiabicyclo[3.1.1]heptane had been added: the nitrile which had been treated with thiacyclobutane was converted almost entirely to solid polymer over the same period.

The sulfide was completely removed from a solution of 6-thiabicyclo[3.1.1]heptane (0.19 g.) in *n*-pentane (2 ml.) by shaking with concentrated sulfuric acid (1 ml.) for about 10 min. The acid layer assumed a yellow color and there was formation of sulfur dioxide. After standing for 2 hr., the acid layer was added dropwise to a cooled solution of potassium hydroxide (2.5 g.) in ice water (10 ml.) covered by a layer of *n*-pentane (10 ml.). Only about 20% of the original sulfide was recovered by evaporation of the *n*-pentane extracts.

Derivatives of the sulfides. The mercuric chloride complex, methiodide, and sulfone of 7-thiabicyclo[2.2.1]heptane were prepared in the usual way. An attempt to prepare the methiodide of 6-thiabicyclo[3.1.1]heptane gave an oil but a solid sulfone was obtained by the usual method. The melting point and analysis of this sulfone is given in Table II

together with the melting points and analyses of the 7-thiabicyclo[2.2.1]heptane derivatives.

Acknowledgment. The authors wish to thank the chairman and directors of The British Petroleum Company Limited for permission to publish these results and Messrs. N. G. McTaggart and A. R. West for the determination of the absorption spectra.

(16) E. Pesch and S. L. Friess, *J. Am. Chem. Soc.*, **72**, 5756 (1950).

SUNBURY-ON-THAMES, ENGLAND

[CONTRIBUTION FROM THE BIOLOGICAL LABORATORIES OF AMHERST COLLEGE]

Reaction of *N*- and *O*-Alkylchelidamic Acids with Thionyl Chloride[1]

D. G. MARKEES*

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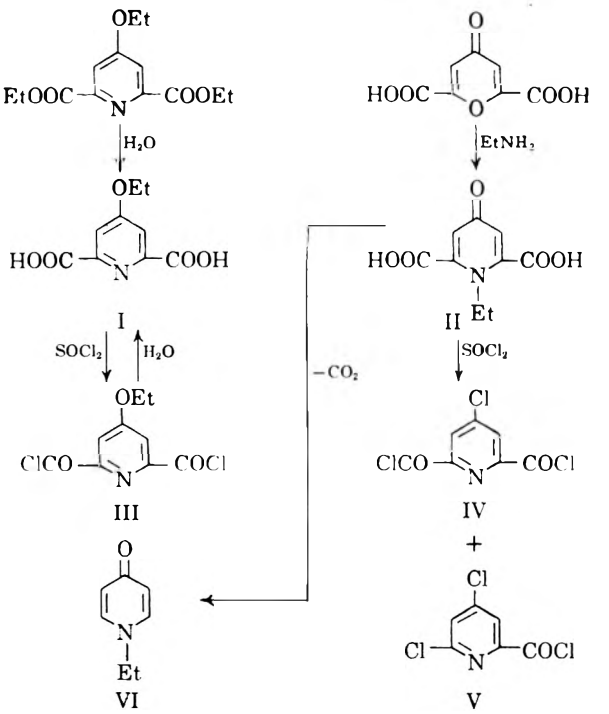
The reactions of *N*-alkyl-4-pyridone-2,6-dicarboxylic acids and of the isomeric 4-alkoxypyridine-2,6-dicarboxylic acids with thionyl chloride are described. The latter yield the expected 4-alkoxypyridine-2,6-dicarboxylic acid chlorides while the former furnish mixtures of 4-chloropyridine-2,6-dicarboxylic acid dichloride and 4,6-dichloropicolinic acid chloride. Derivatives of the various acids are described and some of their physical constants are presented. Also included is the description of *N*-ethyl-4-pyridone.

In a recent publication[2] we described the reaction of sodium ethoxide with diethyl 4-chloropyridine-2,6-dicarboxylate which gave diethyl 4-ethoxypyridine-2,6-dicarboxylate. On hydrolysis of this ester the corresponding acid (I) was obtained. Since its melting point did not agree with the one reported in the literature[3] the isomer *N*-ethyl-4-pyridone-2,6-dicarboxylic acid (II) was prepared for comparison from 4-pyrone-2,6-dicarboxylic acid and ethylamine. Although the formation of the two acids presents in itself some evidence for their constitution, additional proof of structure seemed to be desirable. Their reaction with thionyl chloride was found to serve this purpose. However no conclusions can be drawn as to the structure of the acid prepared by the British authors[3] since their work was not repeated.

On treatment with thionyl chloride, the compound obtained by hydrolysis of diethyl 4-ethoxypyridine-2,6-dicarboxylate gave smoothly the corresponding acid chloride (III) which could be converted to the original acid and to the amide and anilide. On the other hand, the isomer *N*-ethyl-4-pyridone-2,6-dicarboxylic acid (II) gave under comparable conditions a mixture of two products. In addition to the expected[4] 4-chloropyridine-2,6-dicarboxylic acid dichloride (IV) 4,6-dichloropicolinic acid chloride (V) was isolated as the predominant product. Both acid chlorides were characterized by hydrolysis to the parent acids and by conversion to several derivatives.



The literature describes several similar reactions in the pyridine series. It was observed that *N*-methyl-5-methoxy-4-pyridone-2-carboxylic acid reacts with thionyl chloride to give 4,6-dichloro-5-methoxypicolinic acid chloride.[5] An earlier report,[6] however, indicates that the corresponding nor-acid, 5-methoxy-4-pyridone-2-carboxylic acid furnishes 4-chloro-5-methoxypicolinic acid chloride under

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(1) This investigation was supported by a grant (CY-2924) from the National Institutes of Health, U. S. Public Health Service, to Professor G. W. Kidder, whom the author wishes to thank for his continued interest in this work.

(2) D. G. Markees and G. W. Kidder, *J. Am. Chem. Soc.*, **78**, 4130 (1956).

(3) J. N. Collie and G. Bishop, *J. Chem. Soc.*, **127**, 962 (1925).

(4) See *e.g.* H. Maier-Bode and J. Altpeter, *Das Pyridin and seine Derivate in Wissenschaft und Technik*, Wilhelm Knapp, Halle (Saale) 1934, p. 147.

(5) K. Heyns and G. Vogelsang, *Ber.*, **87**, 1377 (1954).

(6) T. Yabuta, *J. Chem. Soc.*, **125**, 575 (1924).

similar conditions. Furthermore, the reaction of picolinic acid with thionyl chloride has been described.[7] On prolonged heating of the components 4-chloropicolinic acid chloride was formed, which under extremely vigorous conditions was converted to 4,6-dichloropicolinic acid dichloride. The much milder conditions under which *N*-alkyl-4-pyridonecarboxylic acids react to give 4,6-dichloropicolinic acid chlorides suggest that a different mechanism is operating in these cases.

The ready loss of one carboxyl group of *N*-ethylchelidamic acid (II) in thionyl chloride prompted an attempt to prepare *N*-ethyl-4-pyridone-2-carboxylic acid by decarboxylation of II under relatively mild conditions. However, the only product which could be isolated after heating II in pyridine in the presence of copper bronze was the picrate of *N*-ethyl-4-pyridone.[8] This pyridone (VI) although mentioned, does not seem to be described adequately in the literature[8,9] and its preparation and some of its physical properties are therefore included.

Finally *N*-methyl-4-pyridone-2,6-dicarboxylic acid[10] and 4-methoxypyridine-2,6-dicarboxylic acid were prepared and subjected to the reaction with thionyl chloride. As expected, 4-methoxypyridine-2,6-dicarboxylic acid dichloride was obtained from the latter, while the former gave a mixture of 4-chloropyridine-2,6-dicarboxylic acid dichloride and 4,6-dichloropicolinic acid chloride. The last two compounds were methanolyzed and identified as methyl esters while 4-methoxypyridine-2,6-dicarboxylic acid dichloride was analyzed as such and furthermore converted to several derivatives, which are included in Table I.

EXPERIMENTAL[11]

4-Ethoxypyridine-2,6-dicarboxylic acid. A mixture of 5.4 g. of diethyl 4-ethoxypyridine-2,6-dicarboxylate[2] and 30 ml. of 10% sodium hydroxide was refluxed for 3 hr. The solid which separated on cooling was filtered, dissolved in 50 ml. of warm water, and the solution acidified with 10% hydrochloric acid. A crop of 2.1 g. (46%) of crude material was obtained. A sample was recrystallized several times from water, dried *in vacuo* at 180° and recrystallized once more from ethyl acetate, m.p. 182–184° (dec.) (Lit.[3] 200°).

Anal. Calcd. for $C_9H_9NO_5$: C, 51.19; H, 4.30; N, 6.64. Found: C, 51.23; H, 4.43; N, 6.57.

4-Methoxypyridine-2,6-dicarboxylic acid. Alkaline hydrolysis of dimethyl 4-methoxypyridine-2,6-dicarboxylate[2] and subsequent acidification gave this acid in 86% yield. A sample was recrystallized from water and obtained as hydrate, m.p. 222.5–223.5° (dec.) after some darkening.

Anal. Calcd. for $C_9H_7NO_5 \cdot H_2O$: C, 44.65; H, 4.22; N, 6.51. Found: C, 44.24; H, 3.93; N, 6.75.

N-Ethyl-4-pyridone-2,6-dicarboxylic acid. A mixture of 1.3 g. of chelidonic acid and 50 ml. of 33% aqueous ethylamine was refluxed for 7 hr. After cooling it was acidified with hydrochloric acid and the precipitate filtered. The yield was 0.6 g. (40%) and a sample recrystallized from water melted at 186–188° if heated slowly and at 196–198° if heated rapidly.

Anal. Calcd. for $C_9H_9NO_5$: C, 51.19; H, 4.30 N, 6.64. Found: C, 51.10; H, 4.41; N, 6.55.

N-Ethyl-4-pyridone. A batch of 11.0 g. of *N*-ethyl-4-pyridone-2,6-dicarboxylic acid was heated in a distillation flask at reduced pressure. An oil of boiling range 190–200°/1–2 mm. distilled over and crystallized on cooling. Repeated distillation gave the analytical sample b.p. 178°/0.8 mm., m.p. 62–64°.[12] This material was sealed immediately after distillation. Exposed to air it becomes liquid accompanied by weight increase.

Anal. Calcd. for C_7H_9NO: C, 68.27; H, 7.37; N, 11.4. Found: C, 67.71; H, 7.25; N, 11.2.

Decarboxylation of N-ethylchelidamic acid (II) *in pyridine.* A mixture of 2.5 g. of *N*-ethylchelidamic acid, 0.5 g. of copper bronze, and 15 ml. of pyridine was refluxed until the evolution of carbon dioxide ceased. The copper catalyst was filtered off, the filtrate evaporated down and the residue taken up with a little water. This solution was treated with charcoal and then with an excess of aqueous picric acid to give a crop of 2.8 g. (67%) of yellow crystals of *N*-ethyl-4-pyridone picrate, m.p. 195–196° (Lit.[8] 196°); no depression of this melting point was observed on admixture with authentic *N*-ethyl-4-pyridone picrate.

4-Ethoxypyridine-2,6-dicarboxylic acid dichloride. A mixture of 2.0 g. of 4-ethoxypyridine-2,6-dicarboxylic acid and 10 ml. of thionyl chloride was heated until a clear, brown solution was obtained. The excess halogenating agent was then removed with the aid of some benzene and upon addition of petroleum benzin a crop of 1.5 g. (64%) of crude crystalline material was obtained. A sample, recrystallized from the same solvent, melted at 77–78°.

Anal. Calcd. for $C_9H_7Cl_2NO_3$: Cl, 28.6; N, 5.65. Found: Cl, 28.5; N, 5.46.

Hydrolysis of this compound produced *4-ethoxypyridine-2,6-dicarboxylic acid* of m.p. 182–184°, undepressed on admixture with an authentic sample.

4-Methoxypyridine-2,6-dicarboxylic acid dichloride. This compound was obtained similarly in nearly quantitative yield. A sample, recrystallized from hexane, melted at 97–99°.

Anal. Calcd. for $C_8H_5Cl_2NO_4$: N, 5.98. Found: N, 5.90.

Hydrolysis of this compound produced *4-methoxypyridine-2,6-dicarboxylic acid* of m.p. 222–224°. No m.p. depression on admixture with an authentic sample was observed.

Reaction of N-ethyl-4-pyridone-2,6-dicarboxylic acid with thionyl chloride. A mixture of 8.0 g. of crude *N*-ethyl-4-pyridone-2,6-dicarboxylic acid and 32 ml. of thionyl chloride was refluxed for 3 hr. The excess thionyl chloride was then removed with the aid of benzene and the residue distilled *in vacuo*. Two fractions of boiling range 92–104°/1.6 mm. (3.2 g., 40%) and of b.p. 117°/1.3 mm. (3.4 g., 38%) were obtained, the latter of which solidified on cooling. Fractionation of the liquid material gave a sample of 4,6-dichloropicolinic acid chloride b.p. 87°/1.3 mm.

Anal. Calcd. for $C_6H_2Cl_3NO$: N, 6.66. Found: N, 6.63.

A sample of the solid product was recrystallized several times from petroleum ether, m.p. 97–98°. Analysis and conversion to derivatives proved it to be *4-chloropyridine-2,6-dicarboxylic acid dichloride.*

Anal. Calcd. for $C_7H_2Cl_3NO_2$: N, 5.87. Found: N, 5.67.

Reaction of N-methyl-4-pyridone-2,6-dicarboxylic acid with thionyl chloride. Refluxing 4.0 g. of *N*-methyl-4-pyridone-2,6-dicarboxylic acid with thionyl chloride furnished, after removal of the excess halogenating agent, 1.9 g. of material

(7) H. Meyer and R. Graf, *Ber.*, **61**, 2210 (1928).

(8) T. Ishii, *J. Pharm. Soc. Japan*, **71**, 1092 (1951).

(9) H. Ost, *J. Prakt. Chem.*, [2] **29**, 378 (1884).

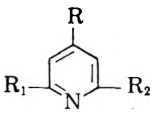
(10) E. R. Riegel and M. C. Reinhard, *J. Am. Chem. Soc.*, **48**, 1334 (1926); E. Spaeth and E. Tschelnitz, *Monatsh.*, **42**, 251 (1921).

(11) All melting points were determined on a Fisher-Johns apparatus and are corrected unless stated otherwise.

(12) Sealed capillary, bath, uncorrected.

TABLE I

DERIVATIVES OF PICOLINIC ACID AND PYRIDINE-2,6-DICARBOXYLIC ACID OF THE STRUCTURE



R	R_1	R_2	Starting Material	Yield,[a] %	M.P.	Recryst. from	Calcd., % N	Found, % N	Empirical Formula
CH_3O	$CONH_2$	$CONH_2$	[b]	90	>300°	H_2O-AcOH	21.5	21.3	$C_9H_9N_3O_3$
CH_3O	$CONHC_6H_5$	$CONHC_6H_5$	[b]	80	275–277°	Dioxane	12.1	11.8	$C_{20}H_{17}N_3O_3$
C_2H_5O	$CONH_2$	$CONH_2$	III	70	289°	H_2O	20.1	20.4	$C_9H_{11}N_3O_3$
C_2H_5O	$CONHC_6H_5$	$CONHC_6H_5$	III	80	258–259°	EtOH	11.7	11.4	$C_{21}H_{19}N_3O_3$
Cl	Cl	COOH	V	80	114–116°[c]	H_2O[d]	7.30	7.11	$C_6H_3Cl_2NO_2$
Cl	Cl	$COOCH_3$	V	90	78.5–79.5°[e]	H_2O-MeOH	6.79	6.48	$C_7H_5Cl_2NO_2$
Cl	Cl	$CONH_2$	V	80	176.5–178.5°[f]	H_2O-EtOH	14.7	14.5	$C_6H_4Cl_2N_2O$
Cl	Cl	$CONHC_6H_5$	V	75	172.5–174.5°	EtOH	10.5	10.3	$C_{12}H_8Cl_2N_2O$
Cl	COOH	COOH	IV	60	218–219°[g]	H_2O	[h]	[h]	$C_7H_4ClNO_4$
Cl	$CONH_2$	$CONH_2$	IV	95	>300°	H_2O	21.1	20.6	$C_7H_6ClN_3O_2$
Cl	$CONHC_6H_5$	$CONHC_6H_5$	IV	65	272°	AcOH	11.9	11.5	$C_{19}H_{14}ClN_3O_2$

[a] Round figures. [b] 4-Methoxypyridine-2,6-dicarboxylic acid dichloride. [c] Lit. 111–112°.[6] [d] Also sublimed *in vacuo*. [e] Lit. 73–74°.[6] [f] Lit. 172–174°.[6] [g] Lit. 220° (dec.).[13] [h] Calcd.: C, 38.28; H, 2.75. Found: C, 38.04; H, 2.86.

boiling up to 110°/4 mm. and 1.0 g. of a residue which solidified on cooling. Samples of the two products were methanolyzed, the former giving *methyl 4,6-dichloropicolinate* of m.p. 78–79°, while the latter yielded *dimethyl 4-chloropyridine-2,6-dicarboxylate* of m.p. 143–144°. No depression of these melting points was observed on admixture with authentic samples.

Derivatives of substituted pyridinecarboxylic acids. The various acid chlorides reported above were converted to a number of derivatives. Hydrolyses and alcoholyses were carried out by mixing the reactants without a solvent. The amides and anilides were prepared by treating benzene solutions of the acid chlorides with ammonia and aniline, respectively. Analyses and more preparative information is contained in Table I.

AMHERST, MASS.

(13) A. P. Sedgwick and N. Collie, *J. Chem. Soc.*, 67, 401 (1895).

[CONTRIBUTION FROM THE ROHM & HAAS COMPANY]

Olefinic Derivatives of 2,4-Diamino-*s*-triazines

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The reaction of *N*-alkylaminoalkyl vinyl ethers with cyanogen chloride gave the corresponding cyanamides. Amidonitriles containing vinyl ether or methacryloyl groups were obtained respectively by the successive cyanoalkylation and acylation of aminoethyl vinyl ether or the reaction of aminonitriles with methacryloyl chloride. Condensation of these cyanamides or amidonitriles with dicyandiamide gave the related derivatives of 2,4-diamino-*s*-triazine, a new group of triazines which undergo addition polymerization.

Olefinic derivatives of 2,4-diamino-*s*-triazines are potentially monomers from which cross-linked polymers may be prepared by successive alternate polymerization procedures. The few compounds of this type which have been described are limited to derivatives having the olefinic group joined directly to the heterocyclic nucleus.[1]

Three new classes of olefinic triazines have been prepared whose common structural feature is separation of the olefin group from the heterocyclic ring by a short chain containing oxygen, nitrogen, or both. Two of these classes are vinyl ethers, the third derivatives of methacrylamide. By appropriate selection of starting materials, a wide variety of monomeric triazines were obtained. These compounds showed good addition polymerization and copolymerization characteristics and could be cured by cross-linking reactions to insoluble polymers.

N-Vinoxyalkylcyanamides (I) were formed by the cyanation of appropriately substituted aminoalkyl vinyl ethers with cyanogen chloride. Subsequent condensation with dicyandiamide in the

(1) J. T. Thurston, U. S. Patent 2,461,943 (Feb. 15, 1949); G. G. Overberger and S. L. Shapiro, *J. Am. Chem. Soc.*, 76, 1061 (1954).

TABLE I

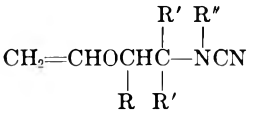
N-ALKYLAMINOALKYL VINYL ETHERS[a]

	B.P., °C(Mm.)	n_D^{25}	d_4^{25}	Nitrogen Calcd.	Nitrogen Found
$C_2H_5NHCH_2CH_2OCH{=}CH_2$	74(87)	1.4277	0.8519	12.2	12.0
$(CH_3)_2CHNHCH_2CH_2OCH{=}CH_2$	79(75)	1.4267	0.8400	10.8	11.2
$CH_3NHCH_2CH(CH_3)OCH{=}CH_2$	76(120)	—	—	12.2	12.1
$(CH_3)_3CNHCH_2CH_2OCH{=}CH_2$	76(43)	1.4282	0.8356	—	[b]
$C_6H_{11}NHCH_2CH_2OCH{=}CH_2$	70(2)	—	—	—	[c]
$(CH_3)_3CCH_2C(CH_3)_2NHCH_2CH_2OCH{=}CH_2$	109(20)	1.4462	0.8515	7.0	6.9
$(CH_3)_3CCH_2CH(CH_3)CH_2NHCH_2CH_2OCH{=}CH_2$	91(2.4)	1.4649	0.8450	6.6	6.5
$NH_2C(CH_3)_2CH_2OCH{=}CH_2$	70(120)	1.4270	0.8498	—	[d]

[a] The compounds and the data were supplied by W. H. Watanabe, Guy Murdoch, and H. J. Schneider, of this laboratory. [b] 98% pure by vinyl ether determination. [c] Crude distillate, 88% pure by vinyl ether determination. [d] 97% pure by vinyl ether titration.

TABLE II

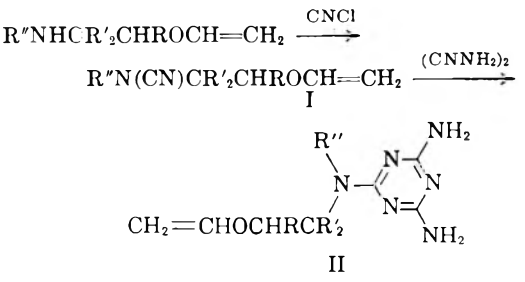
VINOXYALKYLCYANAMIDES



R	R′	R″	Method[a]	Yield, %	B.P., °C.(Mm.)	n_D^{25}	Nitrogen Calcd.	Nitrogen Found
H	H	CH_3	A	93	84–87(1.6)	1.4551[b]	22.2	22.0
H	H	C_2H_5	B	77	85–88(0.3)	1.4535	20.0	19.2
H	H	$(CH_3)_2CH$	B	79	77–78(0.2)	1.4510	18.2	17.9
H	H	$(CH_3)_3C$	A	92	92–95(1.5)	1.4556	16.6	16.4
H	H	C_6H_{11}	A	79	103–105(0.3)	1.4826	14.4	14.3
H	H	$(CH_3)_3CCH_2C(CH_3)_2$	A	70	120–125(0.6)	1.4672	12.5	12.3
H	H	$(CH_3)_3CCH_2CH(CH_3)CH_2$	A	74	128–132(0.5)	1.4577	11.8	11.7
CH_3	H	CH_3	A	90	86–93(0.8)	1.4524	20.0	19.8
H	CH_3	H	A	83	108–110(2)	1.4590[c]	20.0	19.8

[a] Method A: ClCN process; method B: *t*-butylhypochloride—NaCN process. [b] d_{25}^{25} 0.9884. [c] d_{25}^{25} 0.9760.

presence of alcoholic alkali[2] gave 2,4-diamino-6-*N*-alkyl-*N*-vinoxyalkylamino-*s*-triazines (II).



The intermediate cyanamides were obtained in satisfactory yields (Table II). A convenient alternative to the use of cyanogen chloride involved the treatment of mixtures of the amines and aqueous sodium cyanide with *t*-butyl hypochlorite. The cyanamide produced from aminoethyl vinyl ether polymerized at room temperature. The corresponding melamine (II, R, R′, R″ = H) was therefore prepared by the reaction of the amine with 2-chloro-4,6-diaminotriazine.[3] The previously observed stability of secondary *t*-alkyl cyanamides[4] allowed the preparation of a cyanamide (I, R, R″ = H, R′ = CH_3) and its corresponding melamine from 2-amino-2-methylpropyl vinyl ether.

Formation of the substituted melamines (Table VI) was strongly influenced by branching on the carbon atoms immediately adjacent to the amine nitrogen.[5] Excellent yields were obtained from unbranched cyanamides, while moderate branching led to reduced conversion. Frequently unreacted cyanamide could be recovered. The starting cyanamides were quantitatively recovered when the alkyl group (I, R′) was *t*-butyl or 1,1,3,3-tetramethylbutyl.

Another general procedure utilized nitriles (III) obtained by the cyanoalkylation of aminoethyl vinyl ether with cyanohydrins or acrylonitriles (Table III). These aminonitriles could not be converted directly into triazines since they decomposed

(2) W. Zerweck and W. Brunner, U. S. Patent 2,302,162 (Nov. 17, 1942); J. K. Simons, U. S. Patent 2,532,519 (Dec. 5, 1950); D. W. Kaiser, U. S. Patent 2,567,847 (Sept. 11, 1951).

(3) D. W. Kaiser, J. T. Thurston, J. R. Dudley, F. C. Schaeffer, I. Hechenblerkner, and D. Holm-Hansen, *J. Am. Chem. Soc.*, **73**, 2984 (1951).

(4) N. M. Bortnick, U. S. 2,606,923 (May 13, 1950).

(5) L. J. Exner and P. L. de Benneville, *J. Am. Chem. Soc.*, **75**, 4666 (1953).

TABLE III

VINOXYALKYLAMINONITRILES

$CH_2{=}CHOCH_2CH_2NHR$

R	B.P., °C.(Mm.)	Yield	n_D^{25}	Nitrogen Calcd.	Nitrogen Found
$-CH_2CN$	123–128(18)	75	1.4563	22.2	21.8
$-CH(CH_3)CN$	68–72(0.4)	87	1.4503	20.0	19.7
$-CH_2CH_2CN$	79–81(0.4)	70	1.4599	20.0	19.8
$-CH(CN)-CH(CH_3)_2$	77–82(0.6)	93	1.4499	16.7	16.6

TABLE IV

VINOXYALKYLAMIDONITRILES

$CH_2{=}CHOCH_2CH_2N(R)(R')$

R	R′	Yield, %	B.P., °C.(Mm.)	n_D^{25}	Nitrogen Calcd.	Nitrogen Found
CH_2CN	CHO	97	[a]	1.4702	18.2	18.1
	$COOC_2H_5$	100	[a]	1.4546	14.1	13.6
	$COCH_3$	62	113–125(0.25)	1.4760	16.7	16.4
$CH(CH_3)CN$	$COOC_2H_5$	100	[a]	1.4525	13.2	12.9
	$COCH_3$	88	110–115(0.2)	1.4710	15.4	15.3
	COC_6H_5	100	[a]	1.4286	11.5	11.2
CH_2CH_2CN	CHO	100	[a]	1.4880	16.7	16.5
	$COOC_2H_5$	91	107–112(0.2)	1.4590	13.2	13.0
	COC_2H_5	50	125(0.25)	1.4776	14.3	14.3
	COC_6H_5	100	[a]	—	11.5	11.2
	$COC_{15}H_{31}$	86	[a]	—	7.4	7.0
$-CH(CN)-CH(CH_3)_2$	$COOC_2H_5$	97	85–90(0.15)	1.4510	11.7	11.7
$COCH_2CN$	H	99	[a]	1.5242	18.2	17.6

[a] Reaction concentrates.

under the alkaline conditions of the condensation. By blocking the nitrogen atom with an acyl group, however, amidonitriles (IV) were formed which could be converted to triazines. The intermediate amides were prepared by the treatment of the aminonitriles (IV) with acyl chlorides, ethyl chloroformate, or methyl formate (Table IV). Many of these products could not be distilled, but were obtained as high purity crudes which could be used in the condensation with dicyandiamide to give 2,4-diamino-6-*N*-vinoxyethyl-*N*-acylamidoalkyltriazines (V) (Table VII).

$CH_2{=}CHOCH_2CH_2NH_2 \longrightarrow$

$CH_2{=}CHOCH_2CH_2NHCHR[CH_2]_nCN \longrightarrow$

III

$CH_2{=}CHOCH_2CH_2N(COR')CHR[CH_2]_nCN$

IV

$CH_2{=}CHOCH_2CH_2$

$\rightarrow$ $NCHR[CH_2]_n$ — 2,4-diamino-1,3,5-triazin-6-yl (n = 0 or 1)

$R'CO$

V

Compounds of type V are fully substituted amides. However, this was not always required. An amidonitrile was obtained in a single step by the aminolysis of methyl cyanoacetate with aminoethyl vinyl ether and was successfully converted to a triazine containing a partially substituted amide.

Amidonitriles were also used as intermediates for the synthesis of methacrylamidotriazines. The reaction of methacryloyl chloride with aminonitriles[6] gave methacrylamidonitriles (Table V) which were converted without difficulty into the desired 2,4-diamino-6-methacryloamidoalkyl-*s*-triazines.

TABLE V

N-CYANOALKYLMETHACRYLAMIDES

$CH_2{=}C(CH_3)CONR'$

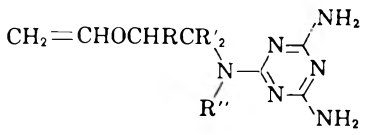
R	R′	Yield	M.P., °C.	Nitrogen Calcd.	Nitrogen Found
H	CH_2CH_2CN	87	46–48	20.3	20.1
H	$C(CH_3)_2CN$[a]	81	102–104	18.4	18.2
CH_3	CH_2CH_2CN	95	[b]	18.4	18.1
C_6H_{11}	CH_2CN	91	73–75	13.6	13.6
C_6H_{11}	CH_2CH_2CN	95	43–44	12.7	12.5

[a] See reference 6. [b] B.p. 113–116°(1 mm.), n_D^{25} 1.4755.

(6) R. Jacobson, *J. Am. Chem. Soc.*, 67, 1996 (1945).

TABLE VI

N-ALKYL-*N*-VINOXYALKYLMELAMINES

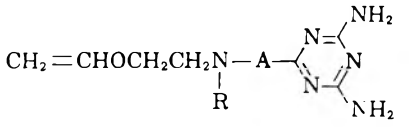


R	R′	R″	Yield, %	M.P.	Nitrogen Calcd.	Nitrogen Found
H	H	H	[a]	148–151	42.8	42.3
H	H	CH_3	83	137–138	40.0	39.9
H	H	C_2H_5	81	141[b]	37.5	37.1
H	H	$(CH_3)_2CH$	28	143–145	38.3	38.5
H	H	C_6H_{11}	42	144–146	30.2	29.8
H	H	$(CH_3)_3CCH_2CH(CH_3)CH_2$	63	72–78	25.3	25.2
CH_3	H	CH_3	50	95–97[c]	37.5	37.4
H	CH_3	H	33	96–98[d]	37.5	37.3

[a] Prepared from diaminochlorotriazine. [b] Recrystallized from 2-butanol. [c] From toluene. [d] From benzene.

TABLE VII

N-VINOXYALKYLAMIDOGUANAMINES



A	R	Yield, %	M.P., °C	Nitrogen Calcd.	Nitrogen Found
$-CH_2-$	CHO	40	194–196[a]	35.3	34.7
	$COOC_2H_5$	84	147–149	29.8	29.5
	$COCH_3$	92	167–168	33.4	32.6
$-CH(CH_3)-$	$COOC_2H_5$	80	140–142	28.4	27.7
	$COCH_3$	62	152–154	31.6	31.0
	COC_6H_5	72	190–193	25.6	25.5
$-CH_2CH_2-$	CHO	90	145–146[a]	33.4	33.4
	$COOC_2H_5$	93	134–136	28.4	28.5
	COC_6H_5	40	156–158	25.6	25.1
	$COC_{14}H_{31}$	63	112–115[b]	18.1	18.4
$>CH[CH(CH_3)_2]$	$COOC_2H_5$	79	141–142[c]	25.9	26.0
$-COCH_2$	H	19	180–182[a]	35.2	35.9

[a] Recrystallized from water; [b] From ethanol; [c] From isopropyl alcohol.

All of the compounds underwent vinyl polymerization and copolymerization in the presence of free radical catalysts. The azo catalysts, α,α'-azodiisobutyronitrile and the azodiisobutyric esters, were particularly useful in the polymerization. The polymers were water-insoluble solids which were solubilized by reaction of the triazine nucleus with formaldehyde. Alkoxyalkyl ethers soluble in common solvents were obtained by acid-catalyzed treatment of these hydroxymethylated polymers with alcohols. Films prepared from these alkoxyalkyl ether polymers catalyzed with strong acids could be insolubilized by heating. Similar effects were observed with copolymers of the triazines with other vinyl monomers, notably acrylic esters and acrylonitrile.

EXPERIMENTAL[7]

Starting materials. Aminoethyl vinyl ether and its homologs were prepared by the addition of acetylene to alkanolamines.[8] The physical properties of hitherto unreported compounds are listed in Table I.

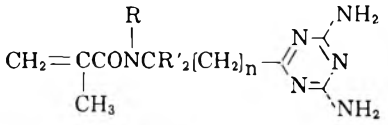
Vinoxyalkylcyanamides (I). (*a*) *N-Methyl-N-2-vinoxyethylcyanamide* (*Method A*). A solution of *N*-methylaminoethyl vinyl ether (404 g., 4 moles) in benzene (1660 ml.) was stirred in a 5-liter, 3-necked round bottom flask fitted with an addition funnel, efficient stirrer, thermometer, and reflux condenser cooled by circulated ice water. A solution of potassium carbonate (300 g.) in water (217 ml.) was added rapidly, followed by liquid cyanogen chloride (246 g., 4.0 moles). The temperature was kept between 10 and 20°. The addition of cyanogen chloride was completed in 75 min.

(7) The assistance of A. J. McFaull, G. E. Gantert, L. J. Exner, and Rita Cerruti in the preparation of specific compounds and to R. P. Fellmann, D. Falgiatore, and L. Souder in polymer preparations is gratefully acknowledged. We are especially indebted to W. H. Watanabe, Guy Murdoch, and H. J. Schneider who supplied the vinyl ethers.

(8) W. Reppe, U. S. Patent 1,959,927 (May 22, 1934); W. Reppe and O. Hecht, U. S. Patent 2,157,347 (May 9, 1939); A. E. Favorskii and M. F. Shostakovskii, *J. Gen. Chem.* (*USSR*), **13**, 1 (1943); W. H. Watanabe and L. E. Conlon, *J. Am. Chem. Soc.*, **79**, 2825 (1957).

TABLE VIII

METHACRYLAMIDOGUANAMINES



R	R'	n	Yield, %	M.P., °C.	Nitrogen Calcd.	Nitrogen Found
H	H	1	78	184–185	37.8	37.0
H	CH_3	0	51[a,b]	175–177[c]	35.6	35.3
CH_3	H	1	64	256–257[d]	35.6	35.4
C_6H_{11}	H	0	82	273–274[d]	29.0	29.0
C_6H_{11}	H	1	68	220–221[d]	27.6	27.5

[a] Recrystallized from water. [b] Monohydrochloride, obtained from 0.5*N* hydrochloric acid, no m.p. below 260°: *Anal.* Calcd. for $C_{10}H_{17}N_6OCl$: Cl, 13.0: found 12.5. [c] Recrystallized from ethanol. [d] From methanol.

After stirring for 2 hr., the slurry was filtered and the solid was washed with benzene. The oil layer obtained from the combined filtrates was distilled to give the oily, colorless product (468 g., 93% yield, b.p. 84–87° (1.6 mm.). The infrared spectrum showed an intense, sharp peak at 2210 cm.$^{-1}$, characteristic of cyanamides, and a strong olefinic band at 1624 cm.$^{-1}$

(*b*) *N-Isopropyl-N-2-vinoxyethylcyanamide* (*Method B*). A solution of 96% sodium cyanide (28.1 g., 0.55 mole) in water (200 ml.) was stirred and cooled in an ice bath at 15°. 2-*N*-Isopropylaminoethyl vinyl ether (64.5 g., 0.5 mole) was added rapidly, then *t*-butyl hypochlorite (60 g., 0.55 mole) during 3 hr., with the temperature held at 15°. After 4 hr. of additional stirring, the oil layer was removed and combined with toluene extracts (3 × 25 ml.) of the aqueous layer. Distillation gave the colorless, oily product which weighed 76 g. (79%), b.p. 77–78% (1.5 mm.).

Vinoxyalkylaminonitriles (III). (*a*) *N-2-Vinoxyethylglycinonitrile.* Glycolonitrile (163 g. of 70% aqueous solution, 2 moles) was added rapidly to aminoethyl vinyl ether (174 g., 2 moles) at 20–30°. After stirring for 5 hr., benzene (300 ml.) was added. The water layer was removed and the benzene solution was distilled to give 190 g. of a colorless oil, b.p. 123–128° (18 mm.). Infrared analysis showed the expected peaks at 3320 (amine stretch), 2235 (C≡N), and 1618 (C=C) cm.$^{-1}$

(*b*) *3-N-2'-Vinoxyethylaminopropionitrile.*[9] Acrylonitrile (106 g., 2 moles) was added to aminoethyl vinyl ether (174 g., 2 moles) with cooling. After 2 hr. of stirring, the orange residue was distilled in two portions after removal of volatile starting materials; the product was obtained as a colorless oil, 196 g., (70%), b.p. 79–81° (0.4 mm.).

N-Vinoxyalkylamidonitriles (IV). (*a*) *N-Vinoxyethyl-α-cyanoacetamide.* The addition of aminoethyl vinyl ether (43.5 g., 0.5 mole) to methyl cyanoacetate (49.5 g., 0.5 mole) was accompanied by the evolution of heat. Methanol (100 ml.) was added and the solution was allowed to stand for several days. Evaporation of solvent under reduced pressure gave 78 g. (100%) of a red, viscous oil.

(*b*) *N-Vinoxyethyl-N-cyanomethylformamide.* Methyl formate (120 g., 2 moles) and *N*-vinoxyethylglycinonitrile (120 g., 1 mole) were refluxed for 8 hrs. Evaporation of excess methyl formate gave a brown oily residue which weighed 150 g. (97%), n_D^{25} 1.4702. The material could not be distilled without extensive decomposition. The reaction concentrate was sufficiently pure for further reaction.

(*c*) *N-Vinoxyethyl-N-β-cyanoethylacetamide.* Acetyl chloride (39.3 g., 0.5 mole) was added slowly to a solution of 3-*N*-β-vinoxyethylaminopropionitrile (70 g., 0.5 mole) and triethylamine (50.4 g., 0.5 mole) in benzene (150 ml.) at 15–25° with cooling. Stirring was continued overnight. The partially solid mixture was filtered; triethylamine hydrochloride was washed with benzene. The combined filtrates were evaporated at reduced pressure to give an oily residue (93 g.), which was distilled to give a pale yellow oil weighing 80.5 g. (88%), b.p. 110–115° (0.2 mm.).

(*d*) *Ethyl N-β-cyanoethyl-N-vinoxyethylcarbamate.* Ethyl chloroformate (95.4 g., 0.88 mole) was added slowly to a mixture of 3-*N*-β-vinoxyethylaminopropionitrile (123 g., 0.88 mole), sodium bicarbonate (74 g., 0.88 mole), and water (275 ml.) at 15–25°. After standing overnight, the mixture was separated. The aqueous layer was extracted twice with 50-ml. portions of chloroform. The extract was combined with the oil layer and the solvent was removed at reduced pressure to give 183 g. (97%) of a red oily residue. Distillation of 60 g. gave 56 g. of a pale yellow oil, b.p. 107–112° (0.2 mm.).

N-Cyanoalkylmethacrylamides. N-Cyclohexyl-N-cyanomethylmethacrylamide. A solution of cyclohexylaminoacetonitrile[10] (138 g., 1 mole) in an equal weight of benzene was added to a solution of methacryloyl chloride (52 g.) in benzene (60 ml.) at 40–50° in 90 min. After stirring three hours longer, the slurry was filtered and the solid washed with benzene. The filtrates were washed with dilute hydrochloric acid and with water. Decolorization with Nuchar and evaporation gave 93 g. of the white solid product, m.p. 73–75°.

Other *N*-alkylmethacrylamidonitriles were prepared by this method. α-Methacrylamidoisobutyronitrile and β-methacrylamidopropionitrile were obtained by the method of Jacobson.[6] The solid collected by filtering the reaction slurry was washed with potassium carbonate to dissolve the aminonitrile hydrochloride, then with water. The crude products, which were insoluble in either benzene or water, were purified by recrystallization from water.

Condensation with dicyandiamide. 2-N-Methyl-N-vinoxyethylamino-4,6-diamino-s-triazine. A slurry of *N*-methyl-*N*-vinoxyethylcyanamide (302 g., 2.4 moles), dicyandiamide (240 g., 2.82 moles), and isopropanol was stirred and heated to reflux. The heating bath was removed and a solution of potassium hydroxide (48 g.) in isopropanol (400 g.) was added in 20 min. Vigorous boiling occurred during the addition of catalyst and was controlled by occasional cooling. Heating and stirring was continued for 6.5 hr. The hot mixture was filtered to remove insoluble materials which were washed with 100 ml. of hot isopropanol. The combined filtrates were cooled. The product which separated was collected and washed with warm water to remove some color and unreacted dicyandiamide. After drying, the crystalline white solid weighed 418 g. (83%), m.p. 137–138°.

Other triazines were prepared in a similar manner. The product often separated in pure state and required no further treatment. In some instances, recrystallization was necessary; the solvents used are indicated in the tables. Analogous melamines bearing a long *N*-alkyl group, such as 3,5,5-trimethylhexyl, were extremely soluble in all organic solvents and the crude reaction product could not be purified.

2,4-Diamino-6-N-vinoxyethylamino-s-triazine. A mixture of aminoethyl vinyl ether (17.4 g., 0.2 mole), 2-chloro-4,6-diaminotriazine (29 g., 0.2 mole), sodium carbonate (11 g.), and water (150 ml.) was heated under reflux for 4 hr. The red solid was collected and washed with water and hot ethyl acetate to give 21 g. (53%) of a slightly tan solid, insoluble in most solvents, m.p. 148–151°.

Anal. Calcd. for $C_7H_{12}N_6O$: N, 42.8. Found: N, 42.3.

Polymerization of 2-N-methyl-N-vinoxyethylamino-4,6-diamino-s-triazine. A solution of 2-*N*-methyl-*N*-vinoxyethyl-

(9) H. Bruson, U. S. Patent 2,601,251 (June 24, 1952) has cited this compound without describing its synthesis or properties.

(10) L. J. Exner, P. L. de Benneville, and L. S. Luskin, *J. Am. Chem. Soc.*, 75, 4841 (1953).

amino-4,6-diamino-*s*-triazine (21.5 g.) in an equal amount of dimethylformamide was heated under nitrogen in a citrate bottle in the presence of dimethyl α,α'-azodiisobutyrate (0.32 g.) at 75° for 16 hr. The polymer was precipitated from the viscous solution on the addition of acetone, and filtered. It was washed with hot acetone and hot isopropyl alcohol to remove monomer. The dry polymer weighed 20 g. (93%). It was insoluble in common solvents, but dissolved in formic or acetic acid and in dilute aqueous mineral acids, using at least equivalent amounts of acid.

Similar polymers were also obtained from *N*-methyl-*N*-2-vinoxypropyl-melamine, *N*-1,1-dimethyl-2-vinoxyethyl-melamine, *N*-cyclohexyl-*N*-vinoxyethylmelamine, and methacrylamidoisobutyroguanamine in 40, 74, 52, and 90% yields, respectively.

Hydroxymethylation of polymer from N-methyl-N-vinoxyethylmelamine. The polymelamine (2.1 g., 0.01 mole) was heated with a solution of 36% aqueous formaldehyde (8.2 g., 0.1 mole) and water (10 ml.) made slightly basic with sodium carbonate. After 10 min. at 80–90° and 10 min. at 60°, the clear solution was cooled and carefully acidified with 10 ml. of 0.5*N* hydrochloric acid (0.005 mole). The resulting solution could be diluted further without separation of insoluble material.

Reaction of hydroxymethylated polymer with alcohols. A solution was prepared as before from the polymelamine (2.1 g.) and 37% aqueous formaldehyde solution (5 g., 0.06 mole). Methanol (about 5 ml.) was added until turbidity appeared and the *p*H was adjusted to 5.0 with formic acid. After heating at 60° for 10 min., more methanol was added and the heating repeated. Evaporation to dryness gave a clear, viscous oil soluble in alcohols.

The resin, when repeatedly evaporated with 13-g. portions of *n*-butanol to remove water and methanol, gave a clear, viscous oil soluble in xylene. The original polymer and its hydroxymethylated derivative are insoluble in xylene.

Copolymer of methyl methacrylate and methacrylamidoisobutyroguanamine. A solution of methyl methacrylate (95 g., 0.95 mole) and methacrylamidoisobutyroguanamine (11.8 g., 0.05 mole) in 2-ethoxyethyl acetate (131 g.) was heated at 100° in a nitrogen atmosphere, using benzoyl peroxide (2 g.) as initiator. Additional initiator (0.4 g. total) in the same solvent (15 g.) was added during the heating period of 4.5 hr. A portion of the final, very viscous solution was treated with excess hot methanol to precipitate polymer. A dry, brittle solid, soluble in ethoxyethyl acetate, was obtained. Analysis indicated that a true copolymer had been produced; N, calcd. 3.9; found, 3.3. A portion of the copolymer solution was mixed with a 40% solution of formaldehyde in butanol (20% by weight of polymer solids) and paratoluenesulfonic acid (1% based on polymer solids). The resultant mixture was filmed and baked at 150° for 30 min. to give films of extreme hardness (8H-Koh-i-noor pencil) and exceptional resistance to lacquer solvents.

Copolymers containing 10 mole per cent of the guanamine were also prepared and possessed similar properties.

PHILADELPHIA, PA.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF BRITISH COLUMBIA]

Reaction of Aromatic Ketoximes with Carbon Monoxide and Hydrogen[1]

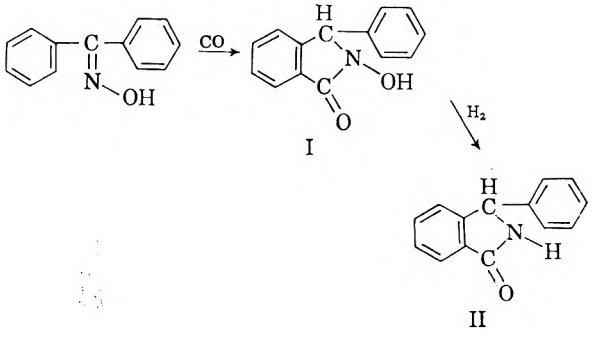
A. ROSENTHAL, R. F. ASTBURY, AND A. HUBSCHER

Received January 10, 1958

A new synthesis of 3-phenyl, 3-methyl, and 3-benzylphthalimidine as well as of 3-phenyl-3,4-dihydroisocarbostyril has been achieved by application of the oxo reaction to aromatic ketoximes. Carbon monoxide and hydrogen also reacted with methyl phenyl ketoxime to give a dimer described tentatively as 3,4-dimethyl-3,4-diphenyl-2-azetidinone. The infrared spectra of the phthalimidines, isocarbostyril, and the dimer product are described.

The oxo reaction[2] is an established procedure for converting olefins to aldehydes or alcohols. The application of this reaction to several aromatic ketoximes is here described.

Benzophenone oxime reacted with carbon monoxide and hydrogen (98.5:1.5) at 4100 p.s.i. and at 250° in the presence of preformed dicobalt octacarbonyl as catalyst to yield 3-phenylphthalimidine (II) in about 80% yield. The structure of II was established by direct comparison with an authentic sample of 3-phenylphthalimidine.[3] Presumably 3-phenylphthalimidine was produced from the expected *N*-hydroxyphthalimidine (I) by reduction



of the latter with hydrogen. The infrared absorption data of 3-phenylphthalimidine are recorded in the experimental. Our observations (absorption at 1675 and 1600 cm.$^{-1}$) agree with the bands for an α-β-unsaturated lactam reported by Edwards and Singh.[4] *o*-Benzoylbenzoic acid oxime also gave 3-phenylphthalimidine in almost quantitative yield.

When methyl phenyl ketoxime reacted with

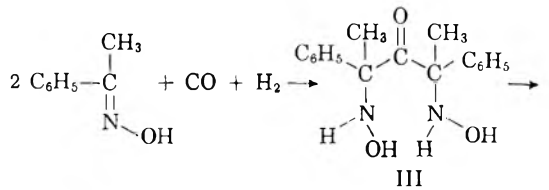
(1) The author (A.R.) is grateful to the National Research Council for the 1956 and 1957 Summer Research Associateships under which part of this work was performed. This investigation was supported in part by a research grant from the National Research Council, Ottawa, Canada.

(2) I. Wender, H. W. Sternberg, and M. Orchin, *Catalysis*, edited by P. H. Emmett, Reinhold Publishing Corp., New York, N. Y., 1957, Vol. 5, p. 73.

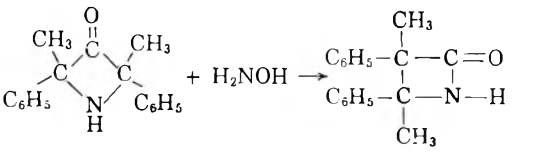
(3) R. E. Rose, *J. Am. Chem. Soc.*, **33**, 388 (1911).

(4) O. E. Edwards and Tara Singh, *Can. J. Chem.*, **32**, 683 (1954).

carbon monoxide and hydrogen a sirup was obtained from which three fractions were isolated by alumina chromatography. As the first fraction (about 10%) contained no carbonyl group, no further work was done on it. Chemical analyses of fraction C indicated that two moles of methyl phenyl ketoxime had condensed with one mole of carbon monoxide and of hydrogen to yield the dimer (III) which then cyclized by splitting out one mole of hydroxylamine. If this is true, the product obtained is either 2,4-dimethyl-2,4-diphenyl-3-azetidinone (IV) or 3,4-dimethyl-3,4-diphenyl-2-azetidinone (V). The rearrangement of



III



IV V

IV to V is typical of the 3-azetidinones.[5] Compound C does not give positive 2,4-dinitrophenylhydrazine and oxime tests but does show strong infrared absorption at 1700 cm.$^{-1}$ which is attributed to the β-lactam structure.[6] Nitrosation of fraction C afforded a bright yellow crystalline *N*-nitroso derivative. It is tentatively suggested, therefore, that the compound's structure is that represented by V. The third fraction (D) was identified as 3-methylphthalimidine[7] by comparison with an authentic sample.

Similarly desoxybenzoin oxime yielded a mixture of two products which were separated by fractional crystallization from ethanol followed by chromatographic purification on alumina. On the bases of chemical and infrared analyses[4] (bands at 3250, 1670 and 1600 cm.$^{-1}$), the minor crystalline component was assumed to be 3,4-dihydro-3-phenylisocarbostyril. The major component was compared with an authentic sample of 3-benzylphthalimidine[8] and shown to be the same.

Two other instances of effecting ring closure with carbon monoxide catalyzed with dicobalt octacarbonyl have recently been reported by Murahashi and Horiie.[9]

We are presently working on the synthesis of *N*-hydroxyphthalimidines by carbonylating aromatic ketoximes.

EXPERIMENTAL[10]

General considerations. The high pressure reactions were carried out in an Aminco Superpressure rocker reaction vessel having a void of 280 ml. The preformed dicobalt octacarbonyl was prepared from cobalt (II) carbonate.[11] The carbon monoxide, obtained from The Matheson Co., East Rutherford, N. J., contained 1.5% hydrogen. The aluminum oxide (calcined) "Analar" was procured from the British Drug Houses (Canada) Ltd., Toronto 14.

Reaction of benzophenone oxime with carbon monoxide and hydrogen to yield 3-phenylphthalimidine. To a solution of benzophenone oxime (14.1 g., 0.07 mole) and dicobalt octacarbonyl (7 g., 0.02 mole) in 25 ml. of purified thiophene-free benzene contained in a glass liner in the bomb was added a mixture of carbon monoxide and hydrogen, (98.5:1.5) at 2070 p.s.i. The bomb was rocked and heated at 250° and 4070 p.s.i. for 6 hr. After the vessel was cooled the pressure was 1915 p.s.i. After the dicobalt octacarbonyl was decomcomposed at 70–80°, the benzene was removed under reduced pressure. Extraction of the solid residue with three 100 ml. portions of ether gave a green solution which upon evaporation gave 2 g. of green colored sirup melting at about −10°. The remaining residue was extracted with hot chloroform to yield 11.6 g. (80%) of material. Recrystallization from ethanol gave 3-phenylphthalimidine, m.p., 218–220°, mixed melting point with an authentic sample of 3-phenylphthalimidine,[3] 218–220°.

Anal. Calcd. for $C_{14}H_{11}NO$: C, 80.37; H, 5.30; N, 6.70; O, 7.64; mol. wt., 209. Found: C, 80.65; H, 5.41; N, 6.86; O, 7.40; mol. wt. (Rast), 233.

Infrared spectrum of 3-phenylphthalimidine in Nujol (cm.$^{-1}$): 3180 (W), 2900 (S), 1675 (S), 1600 (W), 1458 (S), 1375 (S), 1310 (W), 1210 (W), 1040 (W), 953 (W), 918 (W), 783 (M), 730 (S), 695 (M). S, strong; M, medium; W, weak.

The compound was acetylated with acetic anhydride and sodium acetate; m.p., 153–154°; mixed melting point with an authentic sample of 3-phenylphthalimidine acetate,[3] 153–155°.

3-Phenylphthalimidine from o-benzoylbenzoic acid oxime. In a similar way *o*-benzoylbenzoic acid oxime (6.2 g.) was treated with carbon monoxide and hydrogen (4400 p.s.i.) at about 250° with preformed dicobalt octacarbonyl (about 5 g.) in 40 ml. of benzene. After the bomb was cooled to 23°, the observed increase in pressure was about 150 p.s.i. The white crystalline compound (4.6 g.) was extracted from the metallic cobalt present in the product with boiling chloroform, and then thrice recrystallized from ethanol; m.p. 218–220°, mixed melting point with an authentic sample of 3-phenylphthalimidine,[3] 218–220°.

3-Methylphthalimidine and 3,4-dimethyl-3,4-diphenyl-2-azetidinone from methyl phenyl ketoxime. Methyl phenyl ketoxime (13.5 g.) was similarly allowed to react with carbon monoxide and hydrogen (98.5:1.5) at 3800 p.s.i. and at 220° for 4.5 hr. After removal of the catalyst and solvent, a portion of the sirup (1.43 g.) in 5 ml. benzene was added to the top of a glass column containing a 120 × 38 mm. (diam.) adsorbent column of alumina which had been prewashed

(5) H. Staudinger, *Ber.*, **50**, 1035 (1917).

(6) J. C. Sheehan and A. K. Bose, *J. Am. Chem. Soc.*, **72**, 5158 (1950).

(7) S. Gabriel and A. Neumann, *Ber.*, **26**, 705 (1893).

(8) S. Gabriel, *Ber.*, **18**, 1251, 2433 (1885).

(9) S. Murahashi and S. Horiie, *J. Am. Chem. Soc.*, **77**, 6403 (1955); **78**, 4816 (1956).

(10) All melting points were obtained on a Leitz heating stage and are corrected. The infrared analyses were done on a Perkin-Elmer Intracord Spectrophotometer, Model 137, using a sodium chloride crystal. Microanalyses were done by Dr. A. Bernhardt, Mikroanalytisches Laboratorium, im Max-Planck-Institut fur Kohlenforschung, Mülheim (Ruhr), Germany.

(11) I. Wender, H. Greenfield, and M. Orchin, *J. Am. Chem. Soc.*, **73**, 2656 (1951).

with 100 ml. of benzene. The following mixtures of developer were then added consecutively:

(1) 100 ml. benzene which gave 0.14 g. of a colorless sirup A. (A showed no carbonyl band in the infrared.)

(2) 400 ml. benzene-ether (50:50 by vol.) which yielded 0.05 g. of sirup B.

(3) 200 ml. benzene-ethanol (98:2) which gave 0.53 g. of a light yellow sirup C.

(4) 300 ml. benzene-ethanol (90:10) which gave 0.45 g. of solid D.

Fraction D was recrystallized from chloroform-light petroleum ether or from ligroin (b.p. 95–110°), m.p. 110–111°; mixed m.p. of D with an authentic sample of 3-methylphthalimidine,[7] 109–111°.

Fraction C, b.p. 130–140° at 0.01 mm., failed to crystallize from various solvents. After standing at room temperature for 2 months it solidified to a glass. Fraction C did not give a derivative with 2,4-dinitrophenylhydrazine nor with hydroxylamine. Chemical and infrared analyses indicated that C was probably 3,4-dimethyl-3,4-diphenyl-2-azetidinone (V).

Anal. Calcd. for $C_{17}H_{17}NO$; C, 81.30; H, 6.78; N, 5.57; active H, 0.40; mol. wt., 251. Found: C, 81.31; H, 7.10; N, 5.36; active H, 0.44; mol. wt., (Rast) 273.

Infrared spectrum of C in Nujol: 3280 (W), 2920 (S), 1700 (S), 1515 (W), 1460 (S), 1370 (S), 1315 (W), 1215 (M), 1140 (S), 1018 (W), 758 (S), 745 (M), 697 (S).

Treatment of 0.25 g. of fraction C in 6 ml. of glacial acetic acid with excess nitrous acid for 1 hr. according to the procedure of Haworth and Hey[12] gave a bright yellow sirup which crystallized from ether–light petroleum ether; yield, 0.05 g., m.p., 120–122°. This compound was probably 3,4-dimethyl-3,4-diphenyl-1-nitroso-2-azetidinone.

Anal. Calcd. for $C_{17}H_{16}N_2O_2$: C, 72.83; H, 5.75; mol. wt., 280. Found: C, 72.38; H, 5.31, mol. wt. (Rast), 243.

3,4-Dihydro-3-phenylisocarbostyril and 3-benzylphthalimidine from desoxybenzoin oxime. Desoxybenzoin oxime (15 g.) was allowed to react with carbon monoxide and hydrogen (98.5:1.5) in the presence of dicobalt octacarbonyl (7 g.) in 55 ml. benzene at 3600 p.s.i. and 250° for 2 hr. (pressure drop of 200 p.s.i. at room temperature). The (15.9 g.) sirup (Norite) obtained on removal of solvent from the catalyst-free solution was crystallized from 600 ml. of anhydrous ethanol at 0° for 3 hr.; yield 2.5 g. (16%). Pure 3,4-dihydro-3-phenylisocarbostyril was obtained after three recrystallizations from the same solvent; m.p., 202–203°.

Anal. Calcd. for $C_{15}H_{13}NO$: C, 80.69; H, 5.87; O, 7.17; N, 6.28. Found: C, 80.32; H, 6.01; O, 7.54; N, 6.19.

Infrared spectrum of 3,4-dihydro-3-phenylisocarbostyril in Nujol ($cm.^{-1}$) 3250 (W), 2920 (S), 1670 (S), 1600 (W), 1528 (W), 1450 (S), 1375 (S), 1245 (W), 1150 (W), 1070 (W), 1028 (W), 755 (M), 720 (M), 695 (M).

After removal of the ethanol from the filtrate, the sirup was triturated with 500 ml. of ether. A crystalline solid (0.2 g.) was removed by filtration.

The residual sirup obtained after removal of the ether was purified by chromatography on alumina using benzene-anhydrous ethanol (99:1 by vol.) as developer. After removal of the solvent from the eluent the sirup was crystallized from ether-light petroleum ether. Recrystallization from the same solvent pair or aqueous alcohol gave 3-benzylphthalimidine: m.p., 135–136°; mixed m.p. with an authentic sample,[8] 134–136°.

VANCOUVER, CANADA

(12) J. W. Haworth and D. H. Hey, *J. Chem. Soc.*, 361 (1940).

Notes

A department for short papers of immediate interest.

On the Ethanolic Hydrogen Chloride Catalyzed Decarbobenzoxylation of *N*-Carbobenzoxy-DL-methionylglycine Ethyl Ester[1]

OSCAR GAWRON AND FRANK DRAUS[2]

Received September 30, 1957

In this communication the results of experimental work on decarbobenzoxylation of *N*-cbo-DL-methionylglycine ethyl ester[3,4] with ethanolic hydrogen chloride are presented. In keeping with the reaction intermediates and mechanism previously proposed[5,6] for acid-catalyzed decarbobenzoxylations, both *S*-benzyl-DL-homocysteinylglycine ethyl ester and DL-methionylglycine ethyl ester benzyl sulfonium chloride were found as products.

Decarbobenzoxylations were carried out by either refluxing the methionine derivative with ethanolic hydrogen chloride[7] or by heating the derivative with ethanolic hydrogen chloride in a sealed tube. In both cases, it was necessary to find conditions under which decarbobenzoxylation proceeded but which precluded ethanolysis of the peptide bond. Limitation of the reflux period to 30 minutes prevented appreciable peptide bond breaking while a variety of conditions (Table I and Experimental text) under which the peptide bond was stable were found for the sealed tube reactions. In general, at a given temperature, the use of high concentrations of hydrogen chloride resulted in both decarbobenzoxylation and peptide bond breaking while lower concentrations resulted only in decarbobenzoxylation. Our results with *N*-cbo-methionylglycine ethyl ester indicate that the peptide bond of this compound is less stable to refluxing ethanolic hydrogen chloride than that of *N*-cbo-*S*-benzyl-L-cysteinylglycine ethyl ester, the peptide bond of the latter compound being stable to a two-hour reflux period during which time decarbobenzoxylation is effected.[8]

TABLE I

EFFECTS OF ACIDITY ON DECARBOBENZOXYLATION OF *N*-CBO-DL-METHIONYLGLYCINE ETHYL ESTER

11.3*N* HCl, 45°		8.00*N* HCl, 45°		2.17*N* HCl, 77°	
Time, min.	%NH_2-N[a]	Time, min.	%NH_2-N	Time, min.	%NH_2-N
15	1.98	15	1.20	60	1.83
30	2.56	60	1.43	120	2.55
60	4.94	120	2.23	180	3.56
120	5.56	240	3.58	360	3.51
240	5.79			540	3.48

[a] Calculated for DL-methionylglycine ethyl ester benzyl sulfonium chloride, 3.53%.

From decarbobenzoxylations carried out under reflux, *S*-benzyl-DL-homocysteinylglycine ethyl ester was isolated in relatively low yields[9] and from sealed tubes experiments, both *S*-benzyl-DL-homocysteinylglycine and DL-methionylglycine ethyl ester benzyl sulfonium chloride[10,11] were isolated by suitable treatment of the reaction mixture. In one particular experiment, *S*-benzyl-DL-homocysteinylglycine ethyl ester was not isolated following the usual reflux period and isolation procedure. In its place a compound, as yet unidentified, was found.

The replacement of *S*-methyl by *S*-benzyl observed by us also occurs[6] on decarbobenzoxylation of *N*-cbo-DL-methionylglycine with hydrogen bromide in nitromethane. However, decarbobenzoxylation with ethanolic hydrogen chloride also gives rise to a sulfonium derivative while a benzyl sulfonium salt apparently does not form[6] on decarbobenzoxylation of *N*-cbo-DL-methionylglycine with hydrogen bromide in nitromethane. If a benzyl sulfonium derivative is intermediate, in both instances, in the replacement of *S*-methyl by *S*-benzyl, it would seem that the above observed difference is due to differences in stability of the benzyl sulfonium salts in the two reaction media. It might be mentioned here that in aqueous solu-

(1) Abstracted in part from the doctoral thesis of Frank Draus.

(2) Present address, Dept. of Physiology, School of Dentistry, University of Pittsburgh.

(3) Cbo- will be used to designate the carbobenzoxy group.

(4) Prepared from *N*-cbo-DL-methionine and ethyl glycinate by the mixed anhydride procedure of J. R. Vaughn, Jr., and R. L. Osato, *J. Am. Chem. Soc.*, **73**, 5553 (1951).

(5) D. Ben-Ishai and A. Berger, *J. Org. Chem.*, **17**, 1564 (1952).

(6) N. F. Albertson and F. C. McKay, *J. Am. Chem. Soc.*, **75**, 5323 (1953).

(7) Absolute ethanol saturated at room temperature with anhydrous hydrogen chloride. During the reflux period hydrogen chloride is evolved.

(8) S. Goldschmidt and C. Jutz, *Ber.*, **86**, 1116 (1953).

(9) The isolation of DL-methionylglycine ethyl ester benzyl sulfonium chloride was not attempted, albeit chloride to amino nitrogen ratios on the reaction mixture were high, indicating sulfonium salt formation.

(10) As the chloroplatinate.

(11) Under similar conditions, *N*-cbo-DL-methionine ethyl ester yielded mainly DL-methionine ethyl ester benzyl sulfonium chloride.

tion the stability of methionine methyl sulfonium salts depends upon the acid present[12] and that replacement of *S*-methyl with *S*-benzyl has been noted[13] on refluxing methionine with benzyl chloride and hydrochloric acid.

EXPERIMENTAL

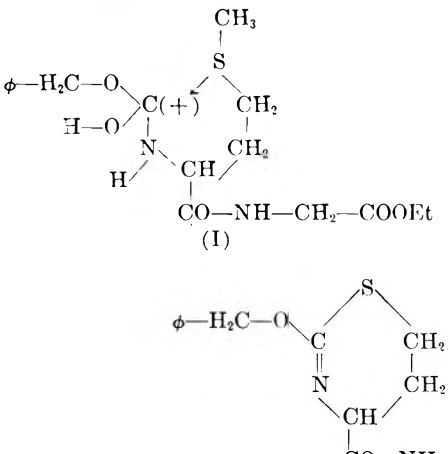
Decarbobenzoxylation by refluxing with ethanolic hydrogen chloride. Kinetic runs. One gram of *N*-cbo-DL-methionylglycine ethyl ester was refluxed for the appropriate period with 20 ml. of anhydrous ethyl alcohol which previously had been saturated at room temperature with anhydrous hydrogen chloride. After refluxing, solvent was removed *in vacuo* at 40° and the residual oil after washing with anhydrous ether was dried *in vacuo* over sodium hydroxide. Amino nitrogen[14] and chloride analyses were performed on the resulting thick oils.

Anal. Calcd. for *S*-benzylhomocysteinylglycine ethyl ester hydrochloride: amino N, 4.05; Cl, 10.23. Found: after 30 min., amino N, 4.07; Cl, 12.9; After 60 min., amino N, 4.64; Cl, 15.0; After 120 min., amino N, 7.35; Cl, 16.7.

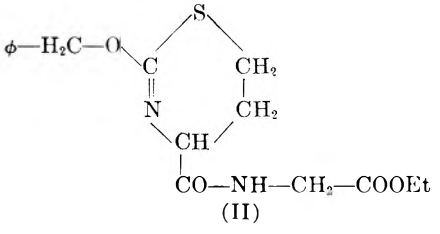
Isolation runs. After refluxing *N*-cbo-DL-methionylglycine ethyl ester with ethanolic hydrogen chloride for 30 min., solvent was removed by distillation *in vacuo* at 40°. The residual oil was dissolved in water and after cooling in an ice bath, sufficient anhydrous potassium carbonate to form a thin paste was slowly added. The oil which came out of solution was extracted with several portions of ether. After washing the combined extracts with water and drying over anhydrous sodium sulfate, the ether extract was concentrated at 40°. From one representative run, 33% of *S*-benzyl-DL-homocysteinylglycine ethyl ester was obtained as an oil.

Anal. Calcd. for $C_{15}H_{22}N_2O_3S$: amino N, 4.52; N, 9.04. Found: amino N, 4.43; N, 8.91.

In one particular run, 12.0 g. of *N*-cbo-DL-methionylglycine ethyl ester yielded 7.1 g. of a thick oil which rapidly solidified and after recrystallization from alcohol-water melted at 81–83°. This compound did not possess a free amino group and after hydrolysis with *N* hydrochloric acid in a sealed tube at 100° for 8 hr., only glycine and *S*-benzylhomocysteine could be demonstrated by chromatography. While further work is necessary for ascertaining the structure of this compound, it is interesting to note that it can be formulated as a dihydrothiazine (II) and formation can be accounted for from intermediate[5,6] (I) by a transacylation mechanism with expulsion of a methyl carbonium ion and loss of water.



(I)



(II)

Anal. Calcd. for $C_{16}H_{20}N_2O_4S \cdot H_2O/2$ (II): C, 55.7; H, 6.09; N, 8.11; S, 9.28; Sap. equiv., 345. Found:[15] C, 55.7: H, 6.11; N, 7.80; S, 9.13; Sap. equiv., 354.

Sealed tube experiments. Kinetic runs. At room temperature 1 g. of *N*-cbo-DL-methionylglycine ethyl ester was dissolved in 10 ml. of ethanolic hydrogen chloride and 1-ml. aliquots were pipetted into a number of tubes. The tubes were then sealed and placed in a water bath. At appropriate time intervals tubes were removed, immediately cooled in an ice bath and then opened. After removal of solvent *in vacuo*, the residual oil was dissolved in water and analyzed for amino nitrogen. The data obtained are presented in Table I.

Chloroplatinate derivative of DL-methionylglycine ethyl ester hydrochloride benzyl sulfonium chloride. One gram of *N*-cbo-DL-methionylglycine ethyl ester was dissolved in 10 ml. of 8.0*N* ethanolic hydrogen chloride and heated in a sealed tube at 45° for 5 hr. After cooling, the tube was opened and 2.5 g. of a 37% solution of platinic chloride in hydrochloric acid was slowly added. The yellow chloroplatinate was filtered off, washed with a small amount of cold, dilute hydrochloric acid and dried *in vacuo*. One gram (50%) of material, decomposing 141–143°, was obtained.

Anal. Calcd. for $C_{16}H_{26}Cl_6N_2O_3PtS$: C, 26.2; H, 3.54; N, 3.82; Pt, 26.6. Found: C, 26.1; H, 3.71; N, 4.10; Pt, 26.9.

S-Benzyl-DL-homocysteinylglycine. *N*-cbo-DL-methionylglycine ethyl ester (4.0 g., 0.011 mole) was heated with ethanolic hydrogen chloride (40 ml., 8.36*N*) at 77° for 1 hr.[16] After cooling, the tube was opened and solvent was removed *in vacuo* at 40°. The residue was dissolved in 50 ml. of methanol and 23 ml. of 1*N* sodium hydroxide was added. After 4 hr., dilute hydrochloric acid was added to neutrality and the solution was then vacuum concentrated to dryness. The residue was extracted with a small amount of cold water to remove soluble salts and then recrystallized from water-ethanol to give *S*-benzyl-DL-homocysteinylglycine (1.0 g., 32%) m.p. 203–205°, lit.,[13] 204°. Neutral equivalent calculated for $C_{13}H_{18}N_2O_3S$: 282. Found: 284.

DL-Methionine ethyl ester hydrochloride benzyl sulfonium chloride. *N*-cbo-DL-methionine ethyl ester (1.0 g., 0.0035 mole) was heated with ethanolic hydrogen chloride (10 ml., 9.6*N*) in a sealed tube at 77° for 7 hr. After cooling, the tube was opened and the contents were concentrated *in vacuo* to an oil. The oil thus obtained was washed with anhydrous ether and after drying *in vacuo* over sodium hydroxide weighed 1.1 g., a 93% yield calculated as the benzyl sulfonium salt.

Anal. Calcd. for $C_{14}H_{23}Cl_2NO_2S$: Cl, 20.9; N, 4.11. Found: Cl, 21.3; N, 4.07.

Since the above sulfonium salt could not be induced to crystallize, it was converted to the dibromide by passage (in ethanol solution) through a column of IRA-410 (Br). After concentration, a residual oil was obtained which could not be induced to crystallize.

Anal. Calcd. for $C_{14}H_{23}Br_2NO_2S$: Br, 37.3; N, 3.26. Found: Br, 37.9, N, 3.54. A solid phosphotungstate could be obtained in 86% yield by the procedure of Lavine *et al.*[12] from the decarbobenzoxylated product.

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(12) T. F. Lavine, N. F. Floyd, and M. S. Cammaroti, *J. Biol. Chem.*, **207**, 107 (1954).

(13) C. A. Dekker and J. S. Fruton, *J. Biol. Chem.*, **173**, 471 (1948).

(14) D. D. Van Slyke, *J. Biol. Chem.*, **83**, 425 (1929).

(15) Analyses by Drs. Weiler and Strauss, Oxford.

(16) Amino nitrogen analysis indicated the liberation of one amino group.

Reversible Oxidation of Guanidinium Ion

SAUL SOLOWAY, HENRY M. ROSENSTOCK,[1] AND ANGELO SANTORO[2]

Received October 18, 1957

Some years ago the senior author and Dr. D. F. Herman[3] attempted a synthesis of 2-aminopyrimidine by condensing guanidine and glycerol in concentrated sulfuric acid solution containing any one of a variety of oxidants.[4] The one reaction mixture from which the desired compound was isolated in poor yield contained potassium persulfate. In that mixture a transient blue color appeared in the early heating stages of the reaction. This paper concerns itself with the nature of that blue intermediate.

Elimination experiments showed that the blue color was due to the oxidation of guanidinium (guanidinous) ion by persulfate ion. 90% Aqueous hydrogen peroxide was an effective susbtitute for potassium persulfate, but no replacement was found for the solvent. Among the many solvents tried were glacial acetic acid, methanesulfonic acid, ethanesulfonic acid, and 20% fuming sulfuric acid. In view of the ineffectiveness of the last solvent it seems that permonosulfuric (Caro's) acid rather than perdisulfuric acid was the active oxidant. Treatment of the blue sulfuric acid solutions with zinc, tin, or hydrogen sulfide resulted in bleaching. The full intensity of color returned on retreatment with an excess of either of the effective oxidants.

Spectrophotometric measurements showed that Beer's law was obeyed at both 613 mμ and 650 mμ on dilution with either concentrated or 20% fuming sulfuric acid. The absorption spectra of solutions made from varying ratios of persulfate to guanidinous ions (0.2/1 to 3.7/1 milliequivalents) were identical, as shown in Fig. 1. These results demonstrated the presence of a single absorbing species.

The stoichiometry of the reaction was studied by measuring the transmission at 650 mμ at room temperature as a function of persulfate concentration at fixed concentrations of the reductant. These experiments were complicated by the slow rate of oxidation of guanidinous ion. This permitted a considerable loss of oxidant by autodecom-

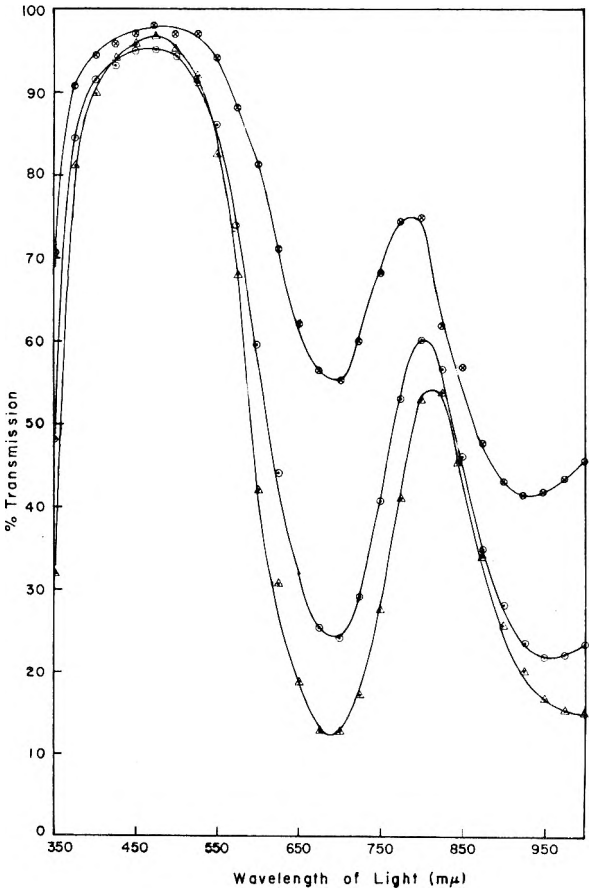


Fig. 1. Absorption spectrum of guanidinic sulfate in sulfuric acid. ⊗ 0.194 milliequivalents of $K_2S_2O_8$ to 5 ml. of 0.185 molar guanidinous sulfate in sulfuric acid. ⊙ 0.744 milliequivalents of $K_2S_2O_8$ to the same volume of reductant solution. △ 2.56 milliequivalents of $K_2S_2O_8$ to the same volume of reductant solution

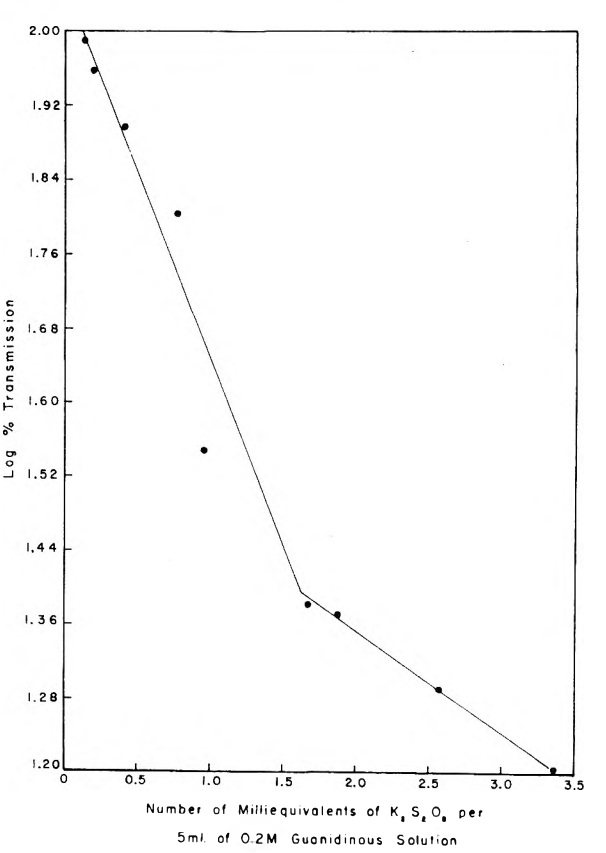


Fig. 2. Extent of oxidation of guanidinous to guanidinic ions by persulfate ion in sulfuric acid

(1) Operations Research, Inc., Silver Spring, Md.

(2) Department of Chemistry, University of Kansas, Lawrence, Kan.

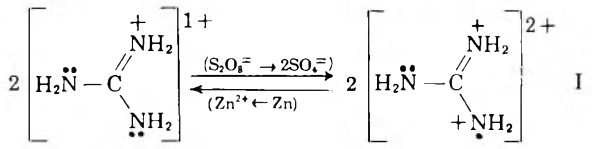
(3) Titanium Division, National Lead Co., Sayreville, N. J.

(4) Unpublished experiments.

position before equilibrium was established. For a 0.2 molar guanidinous solution a break in the absorption curve occurred at a ratio of about 1.6/1 milliequivalents of oxidant/reductant (assumption of one equivalent per mole of reductant) as shown in Fig. 2.

None of the attempts to correct for the autodecomposition of the oxidant proved satisfactory. The addition of an excess of a standard reductant to the concentrated sulfuric acid solution followed by its back titration proved to be an inaccurate measure of total remaining oxidant because the solvent itself contributed to the oxidant capacity. Dilution of the reaction mixture with ice or iced sodium bicarbonate solutions before so measuring total oxidant also gave erratic results. Measurements of the rate of oxygen evolution in a Warburg apparatus offered some promise. However, the rate was complicated by its dependence on product as well as reactant concentrations. In any case, the fact that the break in Figure 2 occurred at an equivalent ratio significantly less than 2/1, coupled with the finding of a single light absorbing species strongly suggests that the oxidation equivalent of guanidinous ion is one electron/mole.

The stability of guanidinic ion in sulfuric acid is understandable in terms of resonance theory. The existence of three symmetrical resonance forms of guanidinous ion "explains" the basic strength of guanidine. In the case of guanidinic ion (I) there are six such forms together with others which make smaller contributions to the state of the ion. The bracketed ions shown below are single resonance forms in which the unbounded electrons and charges have been localized.



I

It is only in such a powerful proton donor as concentrated sulfuric acid that the doubly positive guanidinic ion could exist. Although it seemed improbable that guanidinic ion would dimerize, hydrazine was sought in solutions which were diluted and hydrolyzed. It could not be detected. An attempt was also made to synthesize the unprotonated dimer by condensing cyanamide and hydrazine. It was assumed that if any of the free base were formed, it would dissociate to yield guanidinic ion. No blue color was observed on solution of the reaction mixture in sulfuric acid.

Many attempts to crystallize guanidinic sulfate by cooling its solution with and without the addition of other solvents failed. The addition of water, methanol, acetic acid, or diethyl ether caused immediate bleaching even at $-10°$. Dilution with ether and Dry Ice at $-80°$ resulted in color retention, but fading set in as the solution warmed up. No color remained at $-25°$.

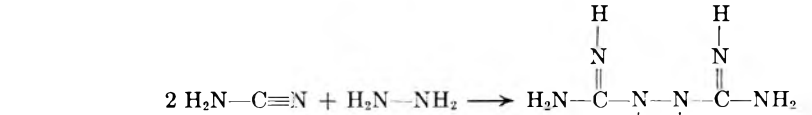
The dilution of the guanidinic sulfate solution with a variety of liquids led to observations of some analytical interest.

1. Dilution with water produced a gas which oxidized iodide ion (potassium iodide paper). The diluted solution contained no guanidinous ion. If a guanidinic solution was first reduced with tin before dilution, guanidinous ion was readily detected.[5]

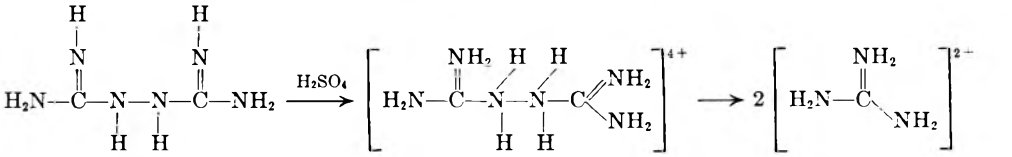
2. Aromatic hydrocarbons and their chlorinated derivatives may be distinguished from alkanes and their chlorinated derivatives. The former group in contrast to the latter reduced guanidinic sulfate, causing a color change from blue to green, orange, or brown.

These experiments were done with guanidinic sulfate solutions which were at least a month old so as to insure the complete absence of permonosulfuric acid. It was established[6] that the latter was but slightly detectable after one week and absent after two weeks at room temperature in concentrated sulfuric acid.

Several derivatives of guanidine were oxidized by permonosulfuric acid in sulfuric acid solution to yield deep red-brown solutions. These were: phenylguanidine carbonate, diphenylguanidine, triphenylguanidine, phenylbiguanide hydrochloride, and *o*-tolylbiguanide hydrochloride. In view of the fact that the common amides and ureas give no such colors on contacts with this reagent, these observations constitute a qualitative test for the guanidine group.



(II)



(III)

(5) Bulletin on sodium β-naphthoquinone-4-sulfonate, Eastman Kodak reagent #1372, Eastman Kodak Co., Rochester, N. Y.

(6) S. Soloway and A. Santoro, *Anal. Chem.*, **27**, 798 (1955).

EXPERIMENTAL

Preparation of guanidinic sulfate and test of Beer's law. Eighteen grams (0.1 mole) guanidine carbonate, purified by recrystallization from water, was dissolved in 100 ml. of ice cold concentrated sulfuric acid. To this solution was added another composed of 27 g. (0.1 mole) potassium persulfate dissolved in 100 ml. of concentrated sulfuric acid. The resulting solution was allowed to warm up to room temperature and stand overnight for full color development. Aliquots were then diluted proportionately with concentrated and 20% fuming sulfuric acids. The per cent transmission at 613 mμ and 650 mμ was determined with a Beckmann DU Spectrophotometer.

Reversibility of the redox system. Aliquots of the above guanidinic sulfate solution were treated with tin, zinc, and anhydrous hydrogen sulfide until almost visually colorless. A brown-pink tint remained in the reduced solutions. The solutions were then reoxidized with excess solid potassium persulfate. The original solution transmitted 3.5% of the incident red light, the reduced solution 96%, and the reduced and reoxidized solution 2%. These measurements were made with a Leitz photoelectric colormeter using filter f-244.

Absorption spectra. To 5 ml. aliquots of a 0.185 molar guanidinous solution were added solid potassium persulfate in amounts equal to 0.103, 0.194, 0.382, 0.744, 0.937, 1.67, 1.85, 2.56, and 3.34 milliequivalents. The per cent transmission of these solutions at various wave lengths was measured with the Beckmann spectrophotometer. For the sake of clarity only three of the family of nine curves are shown in Fig. 1.

Stoichiometry. Weighed quantities of potassium persulfate were added to 5 ml. aliquot of 0.185 molar guanidinous solution. The percent transmission at 650 mμ was again determined with the Beckmann spectrophotometer.

Analytical test for guanidine and derivatives. About 10 mg. of substance were dissolved in 2 ml. of concentrated sulfuric acid. To the resulting solution was added about 30 to 40 mg. of potassium persulfate. On warming or standing at room temperature a blue or deep red-brown color developed.

Test for persulfate and permonosulfate ions.[6] This was identical with the test for phenols with free para positions in which the diluted and neutralized solutions of the above ions were used as the source of oxidant.

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On the Oxidation of Desoxybenzoins

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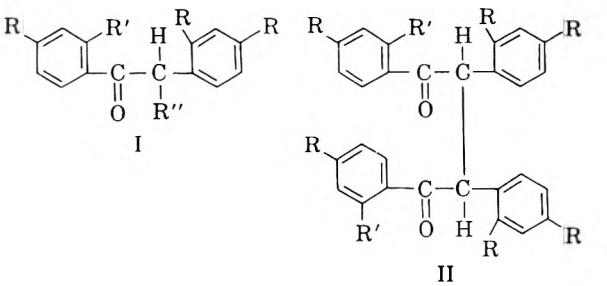
It has been shown[1] by A. Robertson *et al.*, that some desoxybenzoins can be oxidized by potassium permanganate to the corresponding benzoins. Further, it was found by these and other authors that oxidation of some derivatives of flavanone,[2] isoflavanone,[3] and coumaranone[4] by permanganate produced compounds having a hydroxyl group alpha to the carbonyl group.

In the course of investigation[5] on the coloring matter of *Sophora japonica, L.*, potassium permanganate oxidation of 2-hydroxy-2′,4′,4′-trimethoxydesoxybenzoin (I, R = OCH_3, R′ = OH, R″ = H) in refluxing anhydrous acetone produced a compound $C_{34}H_{34}O_{10}$, melting at 226–227°, in a moderate yield. It has now been confirmed that this compound is a bisdesoxybenzoin derivative having the formula (II, R = OCH_3, R′ = OH).



I II

The ultraviolet absorption spectrum (Figure 1, curve c) of this compound showed almost the same shape as that of the parent desoxybenzoin. The

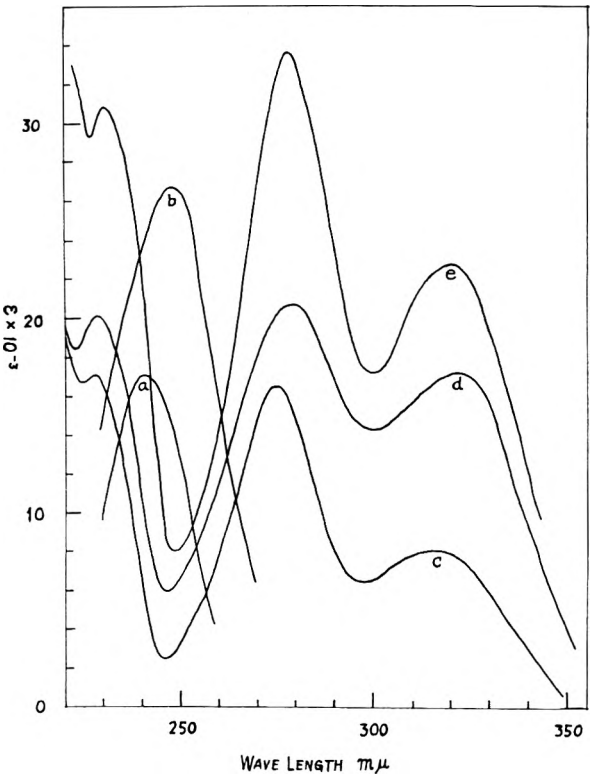


Fig. 1. Ultraviolet absorption spectra: a, Desoxybenzoin; b, Bisdesoxybenzoin; c, 2-hydroxy-2′,4,4′-trimethoxydesoxybenzoin; d, 2-hydroxy-2′,4,4′-trimethoxybenzil; e, Bis-2-hydroxy-2′,4,4′-trimethoxydesoxybenzoin

(1) (a) G. G. Badcock, G. W. K. Cavill, A. Robertson, and W. B. Whalley, *J. Chem. Soc.*, 2961 (1950). (b) After the present work had been completed, the writer received the July 1957 copy of *J. Chem. Soc.* in which Robertson *et al.* showed that the oxidation product of desoxybenzoins was a benzil and not a benzoin as they had previously considered.

(2) A. Robertson and W. B. Whalley, *J. Chem. Soc.*, 1440 (1954).

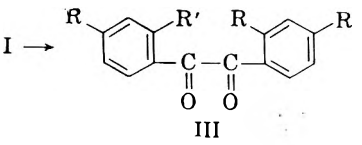
(3) V. B. Mahesh and T. R. Seshadri, *J. Chem. Soc.*, 2503 (1955).

(4) J. Gripenberg, *Acta Chem. Scand.*, **7**, 1323 (1953).

(5) Unpublished paper.

molecular extinction coefficients of the bisdesoxybenzoin maxima, however, were approximately twice those of the latter. Though this compound is indifferent toward ketonic reagents the infrared spectrum showed a strong band of *o*-hydroxyacetophenone system at 1616 cm.$^{-1}$. Because this unexpected product which was not mentioned by the English investigators was obtained, the oxidation of desoxybenzoins by permanganate was examined under various conditions.

Thus, on treatment of (I), (R = OCH_3, R′ = H, R″ = H) by aqueous potassium permanganate at room temperature another compound, $C_{17}H_{16}O_6$ (III), was produced in place of the expected 2-hydroxy-2′,4,4′-trimethoxybenzoin.



III

The following facts indicate definitely that this compound is a derivative of benzil and not of benzoin. The infrared spectrum[6] (Nujol or CS_2) showed no band attributable to a free alcoholic hydroxyl in the region 3000–3500 cm.$^{-1}$. In the ultraviolet spectrum (Figure 1, curve d) the wave lengths of the maxima of compound III and the parent desoxybenzoin I are very similar. However, the extinction coefficients of the maxima of the former are considerably increased in comparison with those of the latter. (In the 332 mμ maximum it is about twice as great.) This high intensity of the former is consistent with the benzil structure. According to Leonard[7] *et al.* the dicarbonyl system in benzil has a skew configuration, in which the two benzoyl units line in planes approximately at right angles to each other and its excited structures giving the major contribution to the absorption are related to those which cause the absorption of the substituted benzaldehyde. The excited structures lead to a similarity in ultraviolet absorption of both compounds and intensify to approximately double the extinction coefficient of the symmetrical benzil in comparison with the corresponding benzaldehyde. Furthermore, in agreement with the above facts this compound gave a quinoxaline derivative. When the oxidation was conducted in refluxing aqueous acetone, thema in product was the bis compound (II), accompanied by a small amount of the corresponding benzil (III).

Furthermore, desoxybenzoin (I, R = R′ = R″ = H) was oxidized with the same amount of permanganate. At room temperature in anhydrous or aqueous acetone benzil was obtained in good yield. At the reflux temperature, however, didesyl[8] (a bisdesoxybenzoin) (II, R = R′ = H), identified by its analyses and infrared and ultraviolet spectra (Figure 1 curve b), was obtained.

It is of interest that in those cases the temperature is the key factor for oxidative coupling although the yield depends partially upon the content of water. It may be considered that the oxidative coupling proceeds through the formation of intermediary aroylarylmethyl radicals.

A description of this type of oxidative coupling,[3,9] using Fenton's reagent, can be found in the literature. However, in the case of permanganate oxidation, examples of dehydrogenative coupling and dehydrogenation are rather few.[10] The formation of a bis-compound from 4,6-diacetoxy-5-methylcoumaran-2-one[11] and a dehydrogenation product[12] from 1,6-diduryl-2,5-dimesityl-1,5-hexadiene-1,6-diol were noted.

EXPERIMENTAL[13,14]

Oxidation of 2-hydroxy-2′,4,4′-trimethoxydesoxybenzoin (a) with powdered potassium permanganate in anhydrous boiling acetone. Finely powdered permanganate (1.08 g., 0.0068 mole) was added to a solution of 2-hydroxy-4,2′,4′-trimethoxydesoxybenzoin (300 mg., 0.001 mole) in anhydrous acetone (14 ml.) in the course of 3 hr. After the removal of the solvent, water (6 ml.) was added to the residue. The aqueous solution was cleared with sulfur dioxide and extracted with three 50-ml. portions of ether. The combined ethereal extracts were washed with aqueous 5% sodium hydrogen carbonate (20 ml.) then with two 20-ml. portions of 2*N* sodium hydroxide and dried. On evaporation of the ether, the yellow oily bis compound (II), R=OCH_3, R=OH) which crystallized quickly, was obtained. The crystals were washed with a small volume of ether and recrystallized from dilute acetone, yielding colorless needles (60 mg.) of product melting at 226–227°.

Anal. Calcd. for $C_{34}H_{34}O_{10}$: C, 67.76; H, 5.69; Mol. wt., 603. Found: C, 67.97; H, 6.01; Mol. wt. 620 (Rast) $[\alpha]_D^{0°}$.

Ultraviolet absorption (Figure 1, curve e) λ_{max} (alcohol) 230, 278, and 321 mμ (ϵ 30900, 33600, and 22880).

An alcoholic solution of this compound exhibited a red-brown color with ferric chloride. It proved to be insoluble in aqueous 2*N* sodium hydroxide but dissolved in sulfuric acid producing a yellow color. In nitric acid, however, it developed a green color. The oximation was tried in pyridine-alcohol solution on the steam bath for 3 hr., but the original compound was recovered unchanged. The reaction of the

(6) As in *o*-hydroxyacetophenone, the infrared spectrum (in nujol) of this alpha-diketone shows the absence of the clear band attributable to a chelated phenolic hydroxyl in the 3000–3500 cm.$^{-1}$ region. [*Cf.* H. L. Hergert and E. F. Kurth, *J. Am. Chem. Soc.*, **75**, 1662 (1953)].

(7) N. J. Leonard, R. T. Rapala, H. L. Herzog, and E. R. Blout, *J. Am. Chem. Soc.*, **71**, 2997 (1949).

(8) E. Knoevenagel, *Ber.*, **21**, 1355 (1888).

(9) J. H. Merz and W. A. Waters, *J. Chem. Soc.*, 2427 (1949).

(10) T. Sakan in Jikkenkagakukoza, Ed., *Chem. Soc. Japan*, Maruzen Co., Ltd., Tokyo **17**, 62 (1957).

(11) D. H. R. Barton and T. Bruun, *J. Chem. Soc.*, 603 (1953).

(12) R. C. Fuson and R. F. Heitmiller, *J. Am. Chem. Soc.*, **75**, 1494 (1953).

(13) Melting points uncorrected.

(14) Microanalyses by Miss N. Fujino, this laboratory.

compound with alcoholic 2,4-dinitrophenylhydrazine hydrochloride was negative.

(b) *With aqueous potassium permanganate at room temperature.* Potassium permanganate (375 mg., 0.0024 mole) in water (15 ml.) was gradually added in 3-ml. portions to a solution of (I) (R = OCH_3, R′ = OH, R″ = H) (150 mg., 0.0005 mole) in acetone (23 ml.) in the course of 30 hr. On evaporation of the acetone, under reduced pressure, manganese dioxide separated, but redissolved on addition of sulfur dioxide. The solution was extracted with two 50-ml. portions of ether and the combined ethereal extracts were treated with two 20-ml. portions of 5% sodium hydrogen carbonate solution. Upon acidification of the combined sodium hydrogen carbonate extracts with dilute hydrochloric acid, a mixture of 2,4-dimethoxybenzoic acid and 2-hydroxy-4-methoxybenzoic acid was obtained. The ether layer, after removal of the acidic fraction, was dried. After removal of the ether 70 mg. of an oily substance remained. It was dissolved in ethanol and on cooling, 2-hydroxy-2′,4,4′-trimethoxybenzil separated in pale yellow prisms. Repeated crystallization from alcohol gave faintly yellow crystals, m.p. 113–114°. On admixture with the parent ketone (m.p. 117–118°) it melted at about 90–95°.

Anal. Calcd. for $C_{17}H_{16}O_6$: C, 64.55; H, 5.10. Found: C, 64.29; 64.79; H, 5.21, 5.18.

The infrared spectrum showed doublet maximum at 1615 and 1595 $cm.^{-1}$, which is attributable to the chelated conjugated dicarbonyl system. The spectrum was lacking in an alcoholic hydroxyl band. Ultraviolet absorption (Figure 1, curve d) λ_{max} (alcohol) 229, 279, and 322 $m\mu$ (ϵ: 20130, 20790, and 17300). The compound slowly dissolves in aqueous sodium hydroxide. In alcohol solution a red-brown color is produced with ferric chloride. The benzil (10 mg.) and *o*-phenylenediamine (4 mg.) in alcohol (0.5 ml.) were heated under reflux for 3 hr. On dilution of the reaction mixture the quinoxaline derivative separated from the dilute alcohol in yellow needles (4 mg.) melting at 170–171°.

Anal. Calcd. for $C_{23}H_{20}O_4N_2$: N, 7.21. Found: N, 7.11.

(c) *With aqueous potassium permanganate in boiling acetone.* Permanganate (300 mg., 0.0019 mole) in water (15 ml.) was added to 2-hydroxy-4,2′,4′-trimethoxydesoxybenzoin (150 mg., 0.005 mole) in boiling acetone (23 ml.) during the course of 3 hr. After evaporation of the acetone under reduced pressure, the solution was cleared with sulfur dioxide and extracted with two 30-ml. portions of ether. The combined extracts were treated as in (b) above. Thus, 2-hydroxy-4-methoxybenzoic acid was obtained. It was purified by recrystallization from water forming needles melting at 153–154°. A mixed melting point with an authentic sample also melted at the same temperature. The yield of the acid obtained was 1 mg. Evaporation of the washed dried ethereal solution, freed from 2-hydroxy-4-methoxybenzoic acid, gave an oily residue which was crystallized from ethanol. Recrystallization from the same solvent gave 21 mg. of colorless needles melting at 226–227°.

This material was identical to compound (II), R = OCH_3, R′ = OH) prepared according to procedure (a). The alcoholic filtrate from the crystallization gave a resinous residue which was redissolved in a small volume of alcohol. On dilution with water and keeping for a few days at room temperature 2-hydroxy-4,2′,4′-trimethoxybenzil separated III. On recrystallization from alcohol 12 mg. of material melting at 113–114° was obtained. This product was identical to the product isolated in procedure (b).

Oxidation of desoxybenzoin. (a) *At room temperature in anhydrous acetone.* Finely powdered potassium permanganate (3 g., 0.019 mole) was added to a solution of desoxybenzoin (1 g., 0.0051 mole) in anhydrous acetone (50 ml.) in the course of 25 hr. After removal of the solvent under reduced pressure, the residue was treated with water (18 ml.). After clearing the aqueous solution with sulfur dioxide, it was twice extracted with ether using 200 ml. and 100 ml., respectively. The combined ethereal extracts, freed from acidic substances (0.56 g.) by two extractions with 20 ml. each of aqueous sodium hydrogen carbonate, were washed with a small volume of water and dried. On evaporation of the ether the residue remaining was crystallized from dilute methanol. Benzil (0.34 g.) was obtained. It was identified by admixture with an authentic specimen.

(b) *At room temperature in hydrous acetone.* Potassium permanganate (3 g., 0.019 mole) in water (120 ml.) was added in 10-ml. portions to a solution of desoxybenzoin (1 g., 0.0051 mole) in acetone (50 ml.) over 3 days. Needles of benzil separated gradually from the solution. After the evaporation of acetone under reduced pressure, the aqueous solution was treated with sulfur dioxide. The needles (0.63 g.) of benzil suspended in the aqueous solution, in almost pure condition, were collected by filtration. Upon treatment of the solution by aqueous sodium hydrogen carbonate benzoic acid (0.38 g., 0.0031 mole) only was obtained.

(c) *In anhydrous boiling acetone.* Powdered potassium permanganate (3 g., 0.019 mole) was added to a solution of desoxybenzoin (1 g., 0.0051 mole) in anhydrous boiling acetone (50 ml.) in the course of 4 hr. After the evaporation of the solvent, water (18 ml.) was added to the residue. The aqueous solution thus obtained was cleared with sulfur dioxide and twice extracted with a 200- and 100-ml. portion of ether. The combined ethereal solution was then treated with two 20-ml. portions of 5% sodium hydrogen carbonate. On acidification of the combined sodium bicarbonate extracts with dilute hydrochloric acid, pure benzoic acid (0.12 g.) was obtained. Evaporation of the dried ethereal solution left after the separation of the acidic fraction gave a brown resinous product which crystallized only partially. This residue was washed with ether and the extract on evaporation left a yellow amorphous powder. The ether insoluble fraction (0.2 g.) was purified from benzene, giving bisdesoxybenzoin in fine prisms, m.p. 250–251°. The infrared spectrum (in Nujol) showed a band at 1667 $cm.^{-1}$ (conjugated C = O). The compound is soluble with difficulty in alcohol and ether but is readily soluble in acetone.

Anal. Calcd. for $C_{28}H_{22}O_2$: C, 86.12; H, 5.68; mol. wt. 390. Found: C, 85.68; H, 5.88; mol. wt. 418 (Rast).

(Analytical sample dried under reduced pressure at 100–110° for 1 hour) ultraviolet absorption (Figure b) λ_{max} in dioxane 248 $m\mu$ (ϵ, 26500).

(d) *In hydrous boiling acetone.* Powdered potassium permanganate (3 g., 0.019 mole) in water (120 ml.) was added to a solution of desoxybenzoin (1 g., 0.0051 mole) in refluxing acetone (50 ml.) in the course of 1 hr. After the reaction mixture was treated as in the case of procedure (b), 0.38 g. of crude benzoic acid was obtained. The neutral fraction (0.9 g.) was washed with ether, leaving crude bisdesoxybenzoin (50 mg.). On recrystallization of this compound from benzene, pure bisdesoxybenzoin was obtained which was identical in every way with a specimen obtained by procedure (c).

Evaporation of the solvent from the above ethereal solution yielded 0.833 g. of product. When this was submitted to distillation at 30 mm., 50 mg. of benzaldehyde was obtained. It was identified through the 2,4-dinitrophenylhydrazone. Isolation of any other product from the residue left after distillation was unsuccessful.

Acknowledgment. The author wishes to thank Professor Tadashi Masamune for his kind interest and encouragement in this work. The writer is also indebted to Professor S. Matsushita and Miss T. Nakata for infrared spectra.

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N,N-Bis(2-cyanoethyl)acrylamide

WALTER HARRY SCHULLER[1] AND DAVID CHESTER GUTH[2]

Received November 22, 1957

The preparation of the new and interesting vinyl monomer, *N,N*-bis(2-cyanoethyl)acrylamide has been accomplished by the cyanoethylation of acrylamide.

$$CH_2{=}CH_2CONH_2 + 2\ CH_2{=}CHCN \xrightarrow[\text{methoxide}]{\text{sodium}} CH_2{=}CHCON(CH_2CH_2CN)_2$$

This reaction was found to proceed smoothly, with a readily controlled evolution of heat, when carried out on a continuous basis at 45° with a reaction period (residence time) of 20 min. Excess acrylonitrile was employed as the solvent and a solution of sodium methoxide in methanol as the catalyst. The reactor effluent was run into a dilute aqueous solution of acetic acid with sufficient acetic acid always present to keep the mixture at *p*H 4–4.5. This treatment effectively quenched side reactions (as well as cyanoethylation) and minimized hydrolysis of the desired product.

Under the conditions described above, the competitive reactions expected were held in check, namely, the addition of methanol to acrylonitrile, and the base-catalyzed polymerization of acrylonitrile, acrylamide, and *N,N*-bis(2-cyanoethyl)-acrylamide itself. The yield of *N,N*-bis(2-cyanoethyl)acrylamide could very likely be increased over that reported herein (54% based on acrylamide) as no effort to obtain a maximum yield was made.

The homopolymerization of *N,N*-bis(2-cyanoethyl)acrylamide and the copolymerization of this monomer with acrylamide and acrylonitrile were found to proceed readily in the presence of free-radical initiators.

N,N-Bis(2-cyanoethyl)acrylamide has been found effective as a plasticizer for polyacrylonitrile.[3] This new vinyl compound may be useful as a comonomer in fields such as synthetic fibers. The presence of four functional groupings in one molecule should also make this compound attractive as a chemical intermediate.

EXPERIMENTAL[4]

Acrylamide was obtained from the New Product Development Department, American Cyanamid Co.

Acrylonitrile. The commerical product, obtained from American Cyanamid Co., was washed with dilute phosphoric acid and fractionated through an efficient column, the middle cut being retained. The fraction contained 0.57% water. For storage purposes, 10 p.p.m. of *tert*-butyl catechol was added. Immediately before use, the stabilized acrylonitrile was passed through a column of activated alumina to remove both the inhibitor and the water present.

Sodium methoxide in methanol. This solution was prepared by dissolving the required amount of sodium metal in methanol.

Preparation of N,N-bis(2-cyanoethyl)acrylamide via a continuous process. The reactor consisted of a 700-ml. glass vessel 4½ in. in diameter, 7 in. high, having a dome cover, and provided 4 in. from the bottom with an overflow spout having an inside diameter of ¾ in. The dome cover was equipped with a stirrer, thermometer, monomer and catalyst feed lines, and a reflux condenser. The reactor was immersed to the overflow spout in a large, constant-temperature bath filled with glycerin. The overflow spout extended horizontally over the side of the constant-temperature bath, at which point the receiving vessel was located. The monomer solution was metered into the reactor by a gear pump. The catalyst-feeding device was a glass, piston-displacement feeder, operated by a clock motor. Both the monomer and the catalyst solutions were delivered at the bottom of the reactor by means of nitrogen pressure.

The monomer solution consisted of a mixture of 15 parts acrylamide and 85 parts acrylonitrile by weight. This represented a 7.55/1 molar ratio of acrylonitrile to acrylamide. The catalyst solution consisted of a 0.5*N* solution of sodium methoxide in methanol. The run was started by simultaneously introducing the monomer solution at a rate of 2180 ml./hr., and the catalyst solution, at a rate of 73 ml./hr. into the empty reactor, with the bath temperature at 45°. (Caution! Violent or explosive polymerization might occur should the temperature be allowed to rise far above 45°.) The temperature of the reaction was maintained at 45° throughout the run. One hundred seventy min. after the start of the run, steady state conditions were considered to have been obtained and the steady state product (SSP) was then collected for a total of 70 min. The SSP was collected in 32-oz. bottles, each of which contained 100 ml. of 0.33*N* acetic acid. The acid mixture was stirred during the collection of product. The *p*H of the acid SSP mixtures was 4–4.5 throughout. The effluent from the first 170 min. was not retained, although it undoubtedly contained a considerable quantity of *N,N*-bis(2-cyanoethyl)acrylamide.

The SSP from all of the 32-oz. bottles was combined, the organic layer washed twice with 500-ml. portions of 0.1*N* hydrochloric acid, and then washed with four 400-ml. portions of water. The washed acrylonitrile solution of the desired product was dried with sodium sulfate. The drying agent was removed by filtration and the filtrate was concentrated under reduced pressure. An aliquot was worked up and the yield of *N,N*-bis(2-cyanoethyl)acrylamide determined to be 40% based on acrylamide used. The work-up of the aliquot involved dissolution of the aliquot in acetone and precipitation, by the addition of methanol, of a yellow solid. This solid was identified as a polymer containing nitrile and amide groups. The yellow solid was removed by filtration and a small quantity of ethyl ether was added. Poly[*N,N*-bis(2-cyanoethyl)acrylamide] precipitated and was removed by filtration. Finally, an excess of ethyl ether was added to the filtrate and *N,N*-bis(2-cyanoethyl)acrylamide was obtained as a pale yellow, waxy precipitate. This was filtered, dried under reduced pressure over calcium chloride, and weighed.

The combined acetic acid layers, hydrochloric acid washings, and water rinses were extracted repeatedly with acrylonitrile, the combined extracts dried with sodium sulfate, filtered, and stripped under reduced pressure. The residue was treated with an excess of ethyl ether and the resulting white, waxy precipitate of *N,N*-bis(2-cyanoethyl)acrylamide collected by filtration, dried under reduced pressure over calcium chloride, and weighed. The yield obtained from

(1) Present address: Elkin Chemical Co., Inc., South Miami, Fla.

(2) Present address: R. T. Vanderbilt Co., Norwalk, Conn.

(3) D. C. Guth and E. J. Kerle, U. S. Patent 2,798,059 (1957).

(4) All melting points and boiling points corrected.

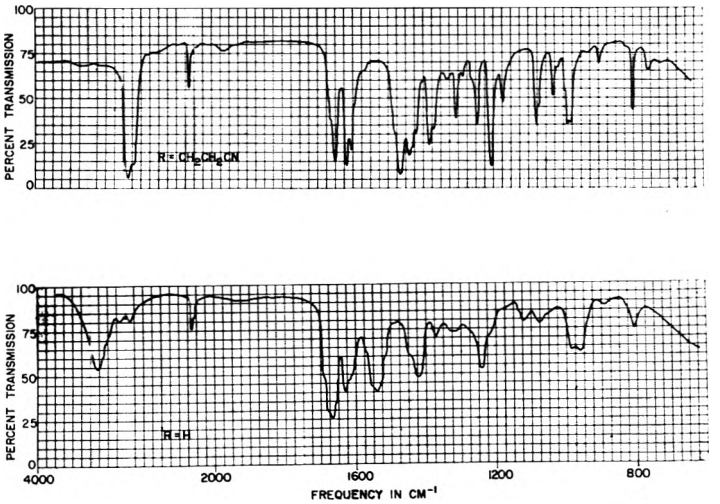

Fig. 1. Infrared spectra of cyanoethylated acrylamides, CH_2=CHCON-(R)CH_2CH_2CN

this fraction was 14.5% based on acrylamide. The total yield was therefore 54.5% based on acrylamide charged to the reaction vessel during the period when SSP was being collected.

A portion of the crude monomer was recrystallized from an acrylonitrile-ethyl ether mixture to the constant m.p. 66.5°.

Anal. Calcd. for $C_9H_{11}N_3O$: C, 61.0; H, 6.22; N, 23.7. Found: C, 60.9; H, 6.30; N, 23.8.

An infrared absorption curve on the pure material confirmed the structure as being that of *N,N*-bis(2-cyanoethyl)-acrylamide. (Fig. 1, R = CH_2CH_2CN.) This monomer was found to be soluble in acetonitrile, acrylonitrile, and hot benzene while insoluble in ethyl ether and cold benzene.

Hompolymerization of N,N-bis(2-cyanoethyl)acrylamide. (a) *Benzoyl peroxide initiator.* To a solution of 1 g. of *N,N*-bis(2-cyanoethyl)acrylamide in 9 g. of benzene was added 0.04 g. of benzoyl peroxide. The clear solution was refluxed for 2 hr. The white insoluble polymer which precipitated from solution during the heating period was filtered, washed thoroughly with fresh benzene, and dried under reduced pressure. The yield of poly-[*N,N*-bis(2-cyanoethyl)acrylamide] was 0.64 g. (64%). This product was insoluble in methanol, water, and benzene. It was soluble in acetonitrile. The polymer softened at 143–144° on a Fisher-Johns melting point apparatus. The specific viscosity of the polymer in dimethyl formamide was 0.30 at 30° (1 g./100 ml.).

(b) *α,α'-Azobisisobutyronitrile initiator.* A 50-ml. round-bottom flask equipped with a reflux condenser was charged with a solution of 2 g. of *N,N*-bis(2-cyanoethyl)acrylamide in 8 g. of benzene and the flask purged with nitrogen for 0.5 hr. To this solution was added 0.04 g. of α,α'-azobisisobutyronitrile and the clear solution was refluxed on a steam bath under nitrogen for 5 hr. The insoluble polymer which formed during this time was collected by filtration, triturated with fresh benzene and air-dried. The yield of poly[*N,N*-bis-(2-cyanoethyl)acrylamide] was 1.4 g. (70%). For purification, the crude product was dissolved in acetonitrile, the solution was filtered by gravity, and the polymer was precipitated by the addition of ethyl ether. This process was carried out twice. The amount of purified polymer recovered was 1 g. An infrared absorption curve on the purified product indicated that little, if any, hydrolysis of the polymer had occurred during polymerization and purification. The molecular weight was found to be approximately 10,000 by microisopiestic measurement. The polymer softened at 163–164° on a Fisher-Johns melting point apparatus. The polymer was insoluble in water, methanol, ethyl ether, and benzene but soluble in acetonitrile.

Anal. Calcd. for $C_9H_{11}N_3O$: N, 23.7. Found: N (Kjeldahl), 22.6, 22.4.

Copolymerization of N,N-bis(2-cyanoethyl)acrylamide with acrylamide. To a 100-ml. round-bottom flask equipped with reflux condenser were added 2 g. of *N,N*-bis(2-cyanoethyl)-acrylamide, 2 g. of acrylamide, and 36 g. of benzene. The solution was purged with nitrogen for 0.5 hr. and 0.08 g. benzoyl peroxide added.

The solution was refluxed under a nitrogen atmosphere for 5.5 hr. The copolymer which precipitated from solution during the reflux period was collected by filtration, triturated with fresh benzene, and air-dried. It weighed 3.6 g. (90%). For purification purposes, it was dissolved in formamide, filtered through a sintered glass funnel and precipitated by pouring into a large excess of ethanol. The precipitate was collected by filtration, washed throughly with ethanol, and dried. The purified polymer softened at 197–199° when heated on a Fisher-Johns melting point apparatus. The Kjeldahl nitrogen content was found to be 20.8%. This would indicate the copolymer to contain about 50% acrylamide on a weight basis. This estimate was confirmed by an analysis of infrared absorption curves.

(b) *Acrylonitrile as a comonomer.* To a 50-ml. round-bottom flask were added 1 g. of *N,N*-bis(2-cyanoethyl) acrylamide, 3 g. of acrylonitrile, and 36 g. of benzene. The mixture was purged with nitrogen under a reflux condenser for 0.5 hr. The solution was then heated under reflux for 5.5 hr. The copolymer which precipitated during the polymerization was filtered, triturated with fresh benzene, and dried. It weighed 2.0 g. (50%). The crude copolymer was dissolved in a small amount of a 1/1 mixture (by volume) of dimethyl formamide and acetonitrile, filtered by gravity, and precipitated by pouring into a large excess of methanol. After filtration and air drying, the copolymer was found to have a Kjeldahl nitrogen content of 24.2%. This corresponded to a 1/1 copolymer on a weight basis. The copolymer softened at 139–142°, on a Fisher-Johns melting point apparatus.

Distillation of N,N-bis(2-cyanoethyl)acrylamide to yield N-(2-cyanoethyl)acrylamide. A 5.0 g. sample of *N,N*-bis(2-cyanoethyl)acrylamide was distilled under reduced pressure in a small all glass low pressure distillation apparatus. At 150° and 1.9 mm. pressure, 2. g. of the material distilled over. The remainder of the product polymerized in the distilling pot to a hard, dark colored glass. A nitrogen analysis of the viscous liquid distillate indicated it to be *N*-(2-cyanoethyl)acrylamide. An infrared absorption spectrum on the distillate lent additional confirmation to this hypothesis (Fig. 1, R = H).

Anal. Calcd. for $C_6H_8N_2O$: N, 22.6. Found: N, 22.3.

Molecular weight: calcd. for $C_6H_8N_2O$, 124. Found: (micro-isopiestic) 150 ± 15.

Acknowledgment. The authors are indebted to Miss E. C. Eberlin for the execution, interpretation, and reproduction of the infrared curves presented herein.

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Reaction of Juglone with Thioglycolic Acid

FRANK G. ROTHMAN[1]

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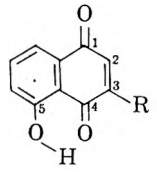
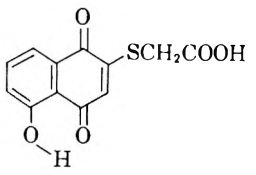
The reaction of excess juglone (Ia) with thioglycolic acid affords only one of the two possible isomeric products, Ib and II, isolated in 73% yield.[2]



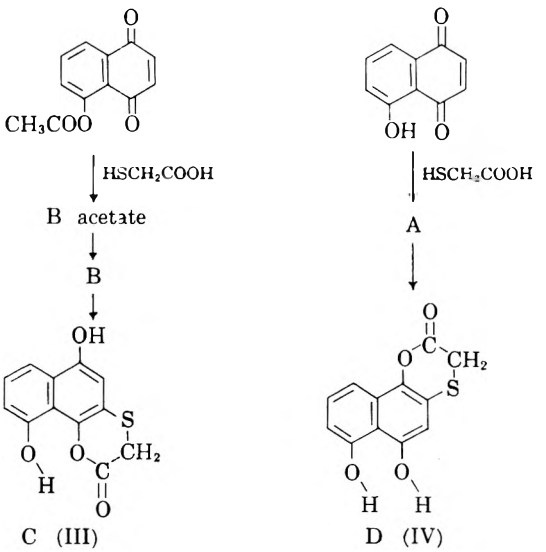
I (a) R = H
(b) R = SCH_2COOH
(c) R = Cl



II

Structure Ib was assigned to this product (A) since it is also formed (in 39% yield) in the reaction of 3-chlorojuglone (Ic) with thioglycolic acid in the presence of pyridine. The reaction of juglone acetate with thioglycolic acid is reported to form only the acetate of the other isomer (B, isolated in 70% yield) to which structure II was assigned by exclusion. Since these results are opposite to those expected for nucleophilic addition,[2,3] and observed for several other reactions, *e.g.* the reaction of 2,3-dibromojuglone and its acetate with aniline,[4] a free-radical mechanism was suggested for the reactions with thiolgycolic acid, and with *p*-thiocresol and *p*-toluenesulfinic acid for which similar results were obtained.[2] No independent evidence was advanced in support of this hypothesis, which does not readily account for the observed orientations. The reaction of thioglycolic acid with 3-chlorojuglone may proceed by attack at either position 2 or 3 (each of which is the β position of an α,β unsaturated carbonyl system) followed by loss of HCl, leading to the formation of either Ib or II or a mixture of both. An unequivocal assignment of structures to the two isomers A and B was therefore desirable. This has been achieved by the reactions summarized in Scheme 1.

Scheme 1



C (III) D (IV)

Catalytic hydrogenation of isomer B,[5] followed by treatment of the crude reaction mixture with *N,N'*-dicyclohexylcarbodiimide[6] afforded compound C, $C_{12}H_8O_4S$, m.p. 193–203° (dec.), which could be identified as III and not IV on the basis of its effect in increasing the acidity of a boric acid solution. While naphthalene derivatives with free hydroxyl groups in the *peri*-positions (*e.g.*, IV) show an effect of unique magnitude in this test,[7] compound C gave only a slight increase (Table I), attributable to the acidity of the phenolic hydroxyl groups. Since compound C is III, structure IV can be assigned to D.

Isomer A on hydrogenation and treatment with *N,N'*-dicyclohexylcarbodiimide was converted into a tan amorphous solid D. The behavior of D in the boric acid test (Table I) is in accord with its formulation as IV.

(1) Present Address: Department of Biology, Massachusetts Institute of Technology, Cambridge 39, Mass. A portion of this work was performed at the Department of Chemistry, University of Wisconsin, Madison, Wis.

(2) R. H. Thomson, *J. Org. Chem.*, **16**, 1082 (1951).

(3) In additions to juglone acetate, conjugation of the unshared electrons of the phenolic oxygen at position 5 with the carbonyl group at position 4 opposes addition to the α,β unsaturated carbonyl system terminating at position 4 and hence 3-substituted derivatives are formed preferentially. This effect is also expected in additions to juglone, but is opposed by the effect of the intramolecular hydrogen bond between the hydroxyl group and the oxygen at position 4, which is expected to favor the accumulation of negative charge in the transition state at O-4 rather than O-2. In the nucleophilic reactions previously reported[2,4] the latter effect predominates.

(4) R. H. Thomson, *J. Org. Chem.*, **13**, 377 (1948).

(5) The infrared spectrum of the residue from the mother liquor of crystallization of B acetate showed the presence of a few per cent of A acetate in the reaction mixture.

(6) *Cf.* R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, and R. W. Kierstead, *J. Am. Chem. Soc.*, **78**, 2023 (1956).

(7) J. Boeseken, J. A. de Bruin, and W. E. van Rijswijk de Jong, *Rec. trav. chim.*, **58**, 3 (1939), *cf.* F. A. Hochstein, C. R. Stephens, L. H. Conover, P. P. Regna, R. Pasternack, P. N. Gordon, F. J. Pilgrim, K. J. Brunings, and R. B. Woodward, *J. Am. Chem. Soc.*, **75**, 5455 (1953).

TABLE I

EFFECTS ON THE ACIDITY OF BORIC ACID[a]

Compound	ΔpH
1,5-Dihydroxynaphthalene	−0.3
1,4,5-Trihydroxynaphthalene	−2.7
C	−0.2[b]
D	*ca.* −2.7[c]

[a] One part (by volume) of a 0.05*M* solution of compound in tetrahydrofuran mixed with one part of 0.5*M* aqueous boric acid. [b] Value extrapolated to zero time (see text). [c] A small portion of compound not in solution.

After aqueous boric acid was added to a solution of C in tetrahydrofuran, the *p*H of the solution decreased gradually (from *ca.* 4.8 to 3.5 in an hour[8]). This change was accompanied by the appearance of a yellow color. These observations are readily explained by hydrolysis of the lactone ring and oxidation to form quinone Ib whose carboxyl group accounts for the decrease in *p*H.[9] After several hours, bronze crystals, m.p. 190–193° (dec.), separated from the solution. The ultraviolet spectrum of this material suggests that it is the quinhydrone of Ib.

The preferential attack of thioglycolic acid at position 2 of juglone and position 3 of juglone acetate are in agreement with predictions for nucleophilic addition[2] and render unnecessary the postulation of a free radical mechanism for these reactions. The directive effect of chlorine substitution in the quinone ring on the course of addition reactions remains to be determined. Preliminary experiments on the reaction of 3-chlorojuglone and its acetate with thioglycolic acid in the absence of pyridine (whose presence permits the possibility of reaction mechanisms involving initial addition of pyridine to the quinone) show that the preponderance of products from reactions other than addition followed by elimination of HCl (*e.g.*, oxidation-reduction) makes these reactions unsuitable for studying this effect. The results of this investigation demonstrate the unreliability of assuming that in stoichiometric replacements of halogen in haloquinones the replacing substituent will occupy the same position as the halogen.

EXPERIMENTAL[10]

Thioglycolic acid (Fisher Scientific Co.) was freshly distilled prior to use.

Ultraviolet spectra were determined in 90% ethanol, 0.01*N* in HCl.

Juglone-2-thioglycolic acid (II). The reaction of juglone with thioglycolic acid was carried out according to the procedure of Thomson[2] who regarded the product as the 3-isomer. The crude product (53%) showed a strong band in the infrared region (in dioxane solution) at 13.05μ which was also found to be present in the spectrum of the recrystallized product, but absent in the spectrum of the 3-isomer. Since no distinctive bands were found in the spectrum of the 3-isomer which are absent in that of the 2-isomer, small amounts of the latter may have escaped detection in the crude material. Recrystallization from ethanol afforded orange-red needles, m.p. 202–205° (dec.) (reported[2] 218°, dec.), λ_{max} 239 mμ (log ϵ 4.17), 251 mμ (log ϵ 4.16), 308 mμ (log ϵ 3.83), and 438 mμ (log ϵ 3.78).

Juglone-2-thioglycolic acid acetate was prepared by acetylation of juglone-2-thioglycolic acid according to the procedure of Thomson[2] who regarded the product as the 3-isomer. Two recrystallizations from benzene afforded fine yellow needles, m.p. 158–161° (reported[2] 174°), $\lambda_{max}^{CHCl_3}$ 5.67, 5.80, 6.00, 6.07, 6.27, 6.33, 6.40, 7.34, 7.51, 7.90, 8.90, 9.08, 11.33, and 11.76μ.

Juglone-3-thioglycolic acid acetate. The reaction of juglone acetate with thioglycolic acid was carried out by adding thioglycolic acid to a solution of juglone acetate in hot ethanol, and allowing the solution to stand overnight. The amounts used and workup was according to the directions of Thomson[2] who regarded the product as the 2-isomer. Three recrystallizations of the crude product (67%) from 60% ethanol gave fine yellow needles, decomposing at 202–203° (reported[2] 217–218°, dec.), $\lambda_{max}^{CHCl_3}$ 5.66, 5.78, 5.99, 6.25, 6.30, 6.38, 6.84, 7.32, 7.50, 7.72, 8.77, 9.13, and 10.40μ. In the infrared spectrum of the residue obtained on evaporation of the mother liquor of the first recrystallization, the intensities of the bands at 7.72μ and 8.78μ were diminished and shoulders at 6.04μ and 7.90μ and a band at 9.08μ appeared.

Juglone-3-thioglycolic acid (Ib). Hydrolysis of juglone-3-thioglycolic acid acetate according to the directions of Thomson,[2] who regarded this as the 2-isomer, gave, after two recrystallizations from 24% aqueous ethanol, fine orange needles, m.p. 202–203° (dec.) (reported[2] 217–218°, dec.), λ_{max} 238 mμ (log ϵ 4.15), 249 mμ (log ϵ 4.11), 308 mμ (log ϵ 3.85), and 414 mμ (log ϵ 3.82).

Reduction of juglone-3-thioglycolic acid and lactonization of the product. Six hundred mg. (2.28 mmoles) of juglone-3-thioglycolic acid (m.p. 202–203°, dec.) was added to a pre-reduced suspension of 0.1 g. precipitated palladium (Palladium Black, Fisher Scientific Co.) in 120 ml. of dioxane. On hydrogenation at room temperature and atmospheric pressure *ca.* 2.7 mmoles (1.2 equiv.) of hydrogen was consumed. The hydrogen was replaced by a nitrogen atmosphere and a solution of 492 mg. (2.28 mmoles) of *N,N'*-dicyclohexylcarbodiimide in 25 ml. of dioxane was added rapidly in order to minimize exposure of the reaction mixture to the atmosphere. The flask was flushed with nitrogen and allowed to stand at room temperature. Colorless crystals (of *N,N'*-dicyclohexylurea) separated after a few minutes. After *ca.* 18 hr. the precipitate was removed by filtration. Lyophilization of the filtrate afforded 693 mg. of a light tan powder. Five hundred and fifty mg. of this product was suspended in 200 ml. of anhydrous ether, the bulk of it dissolving. The mixture was partly decolorized by treatment with 0.3 g. of Norit for 0.5 hr., and after filtration, the yellow solution was brought to dryness at the aspirator. Addition of *ca.* 20 ml. of chloroform to the yellow-tan residue induced crystallization. The yellow crystalline mass was boiled with 250 ml. of chloroform, and after filtration of the hot solution, the residue was boiled with 50 ml. of chloroform. The combined chloroform extracts were evaporated to 100 ml., and fine crystals began to separate: 157 mg. (crop 1) almost colorless needles, m.p. 192–201° (dec.); 30 mg. (crop 2) tan crystals. Recrystallization of crop 1 from chloroform by a similar procedure gave colorless needles, m.p. 193–203° (dec.), λ_{max}^{KBr} 2.8, 3.04, 5.75, 6.13, 6.24, 6.55, 6.77, 6.92, 7.16, 7.33, 7.65, 8.10, 8.62, 8.73, 9.05, 9.46, 10.60, 10.92, 11.18, 11.95, 12.37, 12.50, 13.37, and 13.84μ.

(8) The *p*H of a solvent blank decreased from 4.7 to 4.4 during an equal time interval, presumably due to evaporation of tetrahydrofuran.

(9) No decrease of *p*H with time was observed with D. suggesting that participation of the hydroxyl group at position 5 in C accelerates the hydrolysis of the lactone ring.

(10) Melting points are not corrected. Analyses by Dr. W. C. Alford and associates, National Institute of Arthritis and Metabolic Diseases, Bethesda, Md.

Anal. Calcd. for $C_{12}H_8O_4S$: C, 58.06; H, 3.22; S, 12.91. Found: C, 58.02; H, 3.30; S, 12.97.

Reduction of juglone-2-thioglycolic acid and lactonization of the product. The reduction of juglone-2-thioglycolic acid was carried out in the same manner as reduction of the 3-isomer, using 87 mg. of catalyst and a solution of 355 mg. of the quinone, in *ca.* 125 ml. of dioxane. Lactonization was effected by adding a solution of 288 mg. of *N,N'*-dicyclohexylcarbodiimide in 15 ml. of dioxane to the hydrogenated product under nitrogen. The reaction mixture was worked up in the same way as the 3-isomer, yielding 0.35 g. of a brown powder as the crude product. No crystalline material was obtained on attempted crystallizations from various solvents or chromatography on silicic acid. On sublimation at 160° (*ca.* 0.1 mm.) for a week, about 15% of the crude material was obtained as a very light tan amorphous solid, λ_{max}^{KBr} 5.80, 6.22, 6.35, 6.93, 7.21, 7.30, 7.58, 8.08, 8.20, 8.75, 8.92, 9.07, 9.50, 10.16, 11.06, 11.24, 12.10, 12.20, 12.35, 13.20μ. A second sublimation did not change the infrared spectrum.

Determination of the effect of compounds on the acidity of boric acid. One part (volume) of a 0.05*M* solution of the compound to be tested in tetrahydrofuran was added to one part of 0.5*M* aqueous boric acid solution, and the *p*H was measured on a Beckman *p*H meter, Model G. The *p*H of a blank consisting of one part tetrahydrofuran and one part 0.5*M* boric acid was 4.8–5.2 depending on the sample of tetrahydrofuran used.

A solution of 12.5 mg. (0.05 mmoles) of analytically pure compound D in 1 ml. of tetrahydrofuran was added to 1 ml. of 0.5*M* boric acid. The *p*H decreased from 4.8 to 3.5 in an hour. After the mixture had stood in an open cup for 2.5 hr., bronze crystals, m.p. 190–193° (dec.), λ_{max} 235 mμ ($E_{1\,cm.}^{1\%}$ 71), 252 mμ ($E_{1\,cm.}^{1\%}$ 36), 322 mμ ($E_{1\,cm.}^{1\%}$ 14), 334 mμ ($E_{1\,cm.}^{1\%}$ 15), 350 mμ ($E_{1\,cm.}^{1\%}$ 14), 410 mμ ($E_{1\,cm.}^{1\%}$ 3.6) had separated.

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Reactions of Sodium Phenylacetylide and Sodium Alkoxide with Tosyl and Mesyl Azides[1]

J. H. BOYER, C. H. MACK, N. GOEBEL, AND L. R. MORGAN, JR.

Received December 2, 1957

Six examples of nitrogen singly bound to *sp* carbon have been described in the literature.[2] Current interest in the azidoacetylene unit recognized the possibility for further demonstration of this single bond and for making observations on the properties of this unknown unit.

Initial attempts to prepare phenylazidoacetylene from either phenyliodo- or phenylbromo acetylene and sodium azide were unsuccessful. Attention was then directed to adducts obtained from sulfonyl azides and sodium phenylacetylide since aryl azides had resulted from hydroylsis of triazene salts obtained from aromatic organometallic reagents and tosyl azide.[3] The adduct (I) from sodium phenylacetylide and tosyl azide apparently underwent ring-closure isomerization with the formation of a sodium salt (II) of 1-tosyl-5-phenyltriazole (no triple bond absorption near 4.6 to 4.8μ). Upon hydrolysis linear compounds were not isolated. With equimolar amounts of sodium phenylacetylide and tosyl azide or with an excess of sodium phenylacetylide, a product was obtained to which the structure of 1-tosyl-5-phenyltriazole (III) was assigned,[4] whereas an excess of tosyl

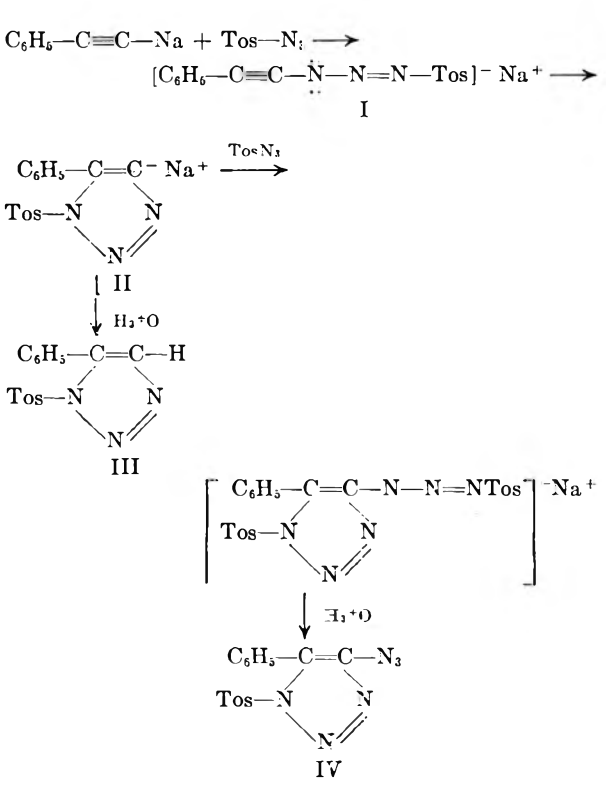
(1) This research was supported by the Office of Ordnance Research, U. S. Army, under Contract No. DA-01-009-ORD-428, a National Institutes of Health Grant No. H-2295, and by a grant from Eli Lilly & Co. Presented at the 131st National Meeting of the American Chemical Society, Miami, April 7–12, 1957.

(2) The observation that 1-aminoacetylenes are probable intermediates in the transformation of substituted propiolic acid amides into fatty acid nitriles by the action of alkaline hypohalite [I. J. Rinkes, *Rec. trav. Chim.*, 46, 268 (1927)] renders unlikely the claim that a 1-aminoacetylene was isolated upon reduction of a 1-nitroacetylene [F. Krafft and G. Heizmann, *Ber.*, **33**, 3586 (1900)]. Trimethylethynylammonium hydroxide [(J. Bode, *Ann.*, **267**, 268 (1890)] and cyanogen azide [A. Angelli, *Atti accad. Lincei*, [6], **5**, 732 (1927); *Chem. Abstr.*, **21**, 3603 (1927)] have been reported and nitroxylnitrile oxide has been considered as an intermediate [R. A. Barnes, "Isoxazoles" in R. C. Elderfield, *Heterocyclic Compounds*, John Wiley, New York, 1957, Vol. 5, p. 459]. An adduct, $[Ar{=}N{=}N{=}N{-}C{\equiv}C{-}N{=}N{=}N{=}Ar]^{-}(MgX)_2^{++}$, obtained from the acetylenic Grignard reagent and aryl azide [H. Kleinfeller and G. Bonig, *J. prakt. Chem.*, **132**, 175 (1932)] contained an eight atom system in conjugation with two aromatic rings over which the π electron density of the doubly charged anion could be spread. Ring closure isomerization also occurred and upon hydrolysis a substituted triazole was obtained along with a bis-acetylenic triazene or its tautomer, $Ar{-}N{=}N{-}N{=}CH{-}CH{=}N{-}N{=}N{-}Ar$.

(3) P. A. S. Smith, private communication. See J. H. Boyer and F. C. Canter, *Chem. Revs.*, **54**, 40 (1954). In contrast hydrolysis of the triazene salt obtained from a sulfonyl azide and the lithium salt of cyclopentadiene led to the formation of diazocyclopentadiene and a sulfonamide [W. von E. Doering and C. H. Depuy, *J. Am. Chem. Soc.*, **75**, 5955 (1953)], a reversal of earlier observations that diazonium salts and sulfonamides reacted with the formation of the expected triazene salt [P. K. Dutt, H. R. Whitehead, and A. Wormall, *J. Chem. Soc.*, **119**, 2088 (1921); P. K. Dutt, *J. Chem. Soc.*, **125**, 1463 (1924); A. Key and P. K. Dutt, *J. Chem. Soc.*, 2035 (1928)].

(4) In 1937 it was claimed [S. G. Fridman and N. N. Lisovskaja, *Zaviski Inst. Khim., Akad. Nauk Ukr. R.S.R., Inst. Khim.*, **6**, 353 (1940); *Chem. Abstr.*, **35**, 2470 (1941)] that sodium phenylacetylide reacted with β-chloroethyl azide with the formation of 4-vinyl-5-phenyltriazole. This required initial attack by the acetylide anion upon carbon, elimination of hydrazoic acid and then recombination presumably by a Diels-Alder reaction to form the disubstituted triazole. The structure proof consisted in oxidation with facile decarboxylation to the known 4-phenyltriazole. Since triazole-4-carboxylic acid did not decarboxylate at temperatures under 210° [O. Baltzer and H. v. Pechmann, *Ann.*, **262**, 317 (1891); O. Dimroth, *Ber.*, **35**, 1044 (1902)], the assignment of the above product as 1-vinyl-5-phenyltriazole is now suggested. Its formation would require initial attack by acetylide ion upon the terminal azido nitrogen, ring-closure isomerization, and hydrolysis. Now, oxidation

azide apparently led to the formation of 1-tosyl-4-azido-5-phenyltriazole (IV) (azide absorption at 4.68μ). Attempts to prepare either III or its isomer, 1-tosyl-4-phenyltriazole, by a Diels-Alder reaction between tosyl azide and phenylacetylene were unsuccessful and it was not possible to obtain 4-phenyltriazole from III since conditions required for hydrolysis were sufficient for rupturing the triazole ring.



Phenylmethanesulfonyl[5] and now methanesulfonyl (mesyl) azides are the known examples of alkanesulfonyl azides. Combination of mesyl azide and sodium phenylacetylide led to intractable tars. Formation of a sodium salt of mesyl azide using sodium metal in ether suggested that attack upon mesyl azide by sodium phenyl acetylide occurred at carbon as well as nitrogen. A strong odor of a volatile azide (presumably methyl azide) was detected during the reaction between sodium methoxide and either mesyl azide or tosyl azide in methanol. In the latter case sodium tosylate was isolated in good yield. Apparently an initial reaction afforded sodium azide and methyl tosylate which subsequently combined to give sodium tosylate and methyl azide. Isolation of *n*-butyl tosylate and sodium azide from tosyl azide and sodium butoxide suspended in ether confirmed the intermediates. Alkylation of sodium azide by alkyl tosylates has been recorded;[6,7] presumably it did not occur in this case because of the insolubility of sodium azide in ether.

$$\text{Tos-N}_3 + \text{NaOR} \longrightarrow \text{NaN}_3 + \text{Tos-OR} \longrightarrow \text{Tos—ONa} + \text{RN}_3$$

EXPERIMENTAL[8,9]

Addition of sodium phenylacetylide to an excess of p-toluenesulfonylazide. Sodium phenylacetylide was prepared from 5.1 g. (0.05 mole) of phenylacetylene in 25 ml. of dry ethyl ether to which 1.15 g. (0.05 mole) of sodium was added slowly. The solution was stirred for 24 hr. A white, ether insoluble solid was separated by filtration and added to 25 ml. of dry ether. This slurry of sodium phenylacetylide in ether was added slowly to a stirred solution of 19.7 g. (0.10 mole) of *p*-toluenesulfonylazide in 50 ml. of dry ether at a rate which maintained an ether reflux. As the reaction mixture was stirred for 24 hr. a brown solid adduct separated, weight 15.2 g. (58%). Infrared absorption (cm.$^{-1}$) from a potassium bromide disk was observed at 3425 (m), 3003 (w), 1597 (w), 1490 (w), 1466 (w), 1443 (w), 1393 (w), 1258 (m), 1198 (s), 1131 (s), 1082 (m), 1046 (s), 1013 (s), 995 (m), 975 (s), 813 (s), 766 (w), 706 (m), 692 (s).

From 5.0 g. of the adduct treated with 10 ml. of hot glacial acetic acid a light yellow solid was obtained upon cooling and was recrystallized twice from glacial acetic acid. The product was assigned the structure of 1-tosyl-4-azido-5-phenyltriazole (IV), 0.52 g. (16%), m.p. 170–171° (dec.). Infrared absorption (cm.$^{-1}$) from a potassium bromide disk was observed at 3425 (w), 3030 (w), 2137 (s) (azide), 1590 (m), 1553 (w), 1527 (w), 1502 (s), 1466 (s), 1445 (s), 1397 (s), 1333 (w), 1309 (m), 1295 (s), 1277 (m), 1190 (s), 1179 (s), 1163 (s), 1118 (w), 1087 (m), 1021 (w), 953 (m), 920 (w), 820 (s), 775 (m), 720 (m), 702 (m), 687 (s), 684 (s), 671 (s). An absorption maximum at 296 mμ (ϵ 31.48) was attributed to the azido group.

Anal. Calcd. for $C_{15}H_{12}N_6SO_2$: C, 52.93; H, 3.55; N, 24.70. Found: C, 53.19; H, 3.63; N, 23.56.

Addition of p-toluenesulfonylazide to an excess sodium phenylacetylide. To 12.5 g. (0.1 mole) of sodium phenylacetylide in 50 ml. of ether, 9.85 g. (0.05 mole) of *p*-toluenesulfonylazide in 50 ml. of ether was added dropwise with stirring and external cooling as the color gradually turned dark brown. The solution was stirred for 12 hr. and saturated with dry hydrogen chloride. Removal of ether left a viscous oil which solidified upon standing for several days. It recrystallized from 95% ethanol as colorless needles of 1-tosyl-5-phenyltriazole monohydrate, 1.5 g. (9.5%), m.p. 171° (dec.).

Anal. Calcd. for $C_{15}H_{15}N_3SO_3$: C, 56.78; H, 4.76; N, 13.24. Found: C, 57.00; H, 5.00; N, 14.04.

Mesyl azide. To a well stirred solution of 11.4 g. (0.10 mole) of methanesulfonylchloride in 40 ml. of absolute methanol was added over a period of one hour in half gram portions,

would bring about the formation of 1-carboxy-5-phenyltriazole, a carbamic acid derivative which would be expected to undergo spontaneous decarboxylation with the formation of 4-phenyltriazole.

(5) T. Curtius and F. W. Haas, *J. prakt. Chem.*, **102**, 85 (1921).

(6) L. Horner and A. Gross, *Ann.*, **591**, 117 (1955).

(7) R. H. Wiley and J. Moffat, *J. Org. Chem.*, **22**, 995 (1957).

(8) Microanalyses by Micro-Tech Laboratories, Skokie, Ill., and Alfred Bernhardt, Mikroanalytisches Laboratorium, Max-Planck-Institut, Mülheim (Ruhr), Germany.

(9) We are indebted to Mr. R. T. O'Connor, Southern Regional Research Laboratory for infrared and ultraviolet absorption data.

8.5 g. (0.13 mole) of solid sodium azide. The solution was stirred for 30 min., filtered, and methanol removed *in vacuo*. Mesyl azide distilled at 56° (0.5 mm.), 7.4 g. (61%). It was thermally unstable above 100° and was not attacked by cold concentrated sulfuric acid whereas rapid decomposition occurred in this solution above 100°. Elemental analysis was not attempted; nitrogen and sulfur were detected by sodium fusion analysis. Infrared absorption ($cm.^{-1}$) from a four per cent chloroform solution was observed at 4310 (w), 4149 (w), 3922 (w), 3546 (w), 3279 (w), 3021 (w), 2924 (w), 2500 (w), 2336 (m), 2137 (s) (azide), 1613 (w), 1449 (w), 1406 (m), 1361 (s), 1326 (s), 1156 (s), 1095 (w), 1003 (m), 966 (s).

For methanesulfonyl chloride, d_{20} = 1.4805; n_D^{20} 1.4464; M_R (obs.) 20.65. This allowed an assignment of 14.68 as the M_R contribution from the methanesulfonyl group. For methane-sulfonyl azide, d_{20} = 1.4024; n_D^{20} 1.4532; M_R (calcd.) 23.58, M_R (obs.) 23.35.

Reaction of p-toluenesulfonylazide with sodium alkoxide. To a solution of 2.3 g. (0.10 mole) of sodium in 160 ml. of absolute methanol, 19.7 g. (0.10 mole) of tosyl azide was slowly added with stirring. The mixture was heated at reflux temperature for 24 hr. as an azide odor was detected and colorless crystals of sodium tosylate, 19.0 g. (98%), separated. From 1.0 g. of this salt suspended in 5 ml. of absolute ether saturated with dry hydrogen chloride a colorless precipitate of *p*-toluenesulfonic acid was obtained, m.p. 104°[10] after recrystallization from benzene. The m.p. of its *o*-toluidine salt was 190°.[11]

The reaction was repeated with 14.4 g. (0.15 mole) of sodium butoxide in 200 ml. refluxing ether. A solution of 19.7 g. (0.10 mole) of tosyl azide in 50 ml. of ether was added dropwise with stirring. The mixture was held at reflux temperature for 12 hr., cooled, and filtered. The solid, 5.3 g. (81.5%), was identified as sodium azide by a positive azide test with ferric chloride solution. An oil residue, 10.4 g. (46%), from the ether layer was dried over anhydrous sodium sulfate and identified as *n*-butyl tosylate, b.p. 100° (0.2 mm.)[12] and n_D^{25} 1.5042.[12] After storage in the refrigerator in a stoppered bottle for four weeks redistillation of 8.0 g. was attempted at 0.2 mm. When the heating bath was at about 70° a violent explosion occurred. The ester apparently had become contaminated with the corresponding acid since a fine white precipitate was noted in the distillation flask just prior to the explosion.[13] A portion of *n*-butyl tosylate was hydrolyzed to *p*-toluenesulfonic acid, m.p. and mixture m.p. 106–107°.[10]

Reaction of methyl tosylate with sodium azide in methanol. To a solution of 18.6 g. (0.1 mole) of methyl tosylate in 160 ml. of absolute methanol was added 6.5 g. (0.1 mole) of solid sodium azide. With efficient stirring the reaction mixture was refluxed for 24 hr. during which time an azide odor was detected. Solid sodium tosylate, 15.4 g. (80%), was separated from the cold mixture and identified by the m.p. and mixture m.p. 104° for the corresponding acid monohydrate and m.p. and mixture m.p. 190° for its *o*-toluidine salt.

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(10) K. H. Slotta and W. Franke, *Ber.*, **63**, 678 (1930).

(11) N. D. Cheronis and J. B. Entrikin, *Semi-micro Qualitative Organic Analysis*, T. Y. Crowell, New York, 1947, pp. 442–444.

(12) H. Gilman and N. J. Beaber, *J. Am. Chem. Soc.*, **47**, 518 (1925) reported b.p. 163–165° (3.0 mm.) and n_D^{20} 1.5050. K. Slotta and W. Franke[10] reported b.p. 146° (1.0 mm.) and 191–192° (17 mm.).

(13) H. Gilman and N. J. Beaber[12] reported that decomposition rapidly commenced after this precipitation became evident. They found that *sec*-butyltosylate decomposed without distilling.

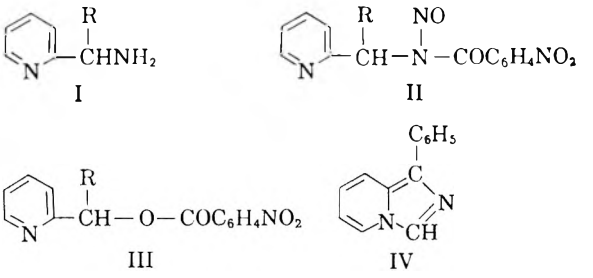
Diazotization of 2-Pyridylmethyl Amine[1]

J. H. BOYER AND L. T. WOLFORD[2]

Received December 6, 1957

An oxidation was observed upon attempted diazotization of 2-pyridylmethyl amine (I, R = H).[3,4] The pyrolysis of *N*-*p*-nitrobenzoyl-*N*-nitroso-2-pyridylmethyl amine (II, R=H) into 2-pyridylmethyl *p*-nitrobenzoate (III, R=H) has now been realized and offers a more successful method for the transformation of this amine into the corresponding carbinol. An *N*-nitroso derivative of *N*-benzoyl phenyl(2-pyridyl)methyl amine could not be obtained.

Catalytic reduction of α-cyanopyridine and the oxime of 2-benzoylpyridine are efficient methods for the synthesis of 2-pyridylmethyl amine and phenyl(2-pyridyl)methyl amine, respectively. A Leuckhart reduction of 2-benzoylpyridine apparently occurs with cyclization and the formation of a product to which the structure of 1-phenyl-2:3a-diazaindene (IV) has been assigned.[5] Attempted reduction of phenyl 2-pyridyl ketoxime with zinc and acetic acid is unsuccessful.[6]



(1) Partial support of this work under National Institutes of Health Grants Nos. H-2295 and CY-2895 is gratefully acknowledged. Presented at the 133rd Meeting, American Chemical Society, San Francisco, April 1958.

(2) Texas Eastman Fellow, 1955–1956.

(3) J. H. Boyer, R. Borgers, and L. T. Wolford, *J. Am. Chem. Soc.*, **79**, 678 (1957).

(4) C. Niemann, R. N. Lewis, and J. T. Hays, *J. Am. Chem. Soc.*, **64**, 1679 (1942) reported a successful diazotization of 2-pyridylmethyl amine in the presence of concentrated hydrochloric acid.

(5) Cyclization during Leuckart reductions of aromatic acyloins was found to be general and produced 4,5-diarylimidazoles [A. Novelli, *Anales Asoc. quim. Arg.*, **27**, 161 (1939); *Chem. Abstr.*, **34**, 1659 (1940)]. W. H. Davies and A. T. Rogers, *J. Chem. Soc.*, 126 (1944). Upon heating α-hydrazinopyridine with formic acid a similar ring closure brought about the formation of 1,2,4-pyridotriazole [R. G. Fargher and R. Furness, *J. Chem. Soc.*, **107**, 688 (1915); see reference 4]. In a similar reaction, 2:3a-diazaindene was prepared by cyclization with dehydration using phosphoryl chloride of *N*-formyl 2-pyridylmethyl amine [J. D. Bower and G. R. Ramage, *J. Chem. Soc.*, 2834 (1955)].

(6) F. B. LaForge, *J. Am. Chem. Soc.*, **50**, 2484 (1928) successfully reduced phenyl 3-pyridyl ketoxime by this method.

EXPERIMENTAL[7]

Phenyl 2-pyridyl ketoxime, m.p. 126–140°, as a mixture of the geometrical isomers, was prepared from 2-benzoylpyridine.[8]

According to the method of Kolloff and Hunter,[9] α-cyanopyridine was reduced, using Raney nickel,[10] to *2-pyridylmethyl amine*, b.p. 102–104° (26 mm.)[11] in 57% yield.

In a similar procedure phenyl 2-pyridyl ketoxime was hydrogenated over 24 hr. The product, *phenyl-2-pyridylmethyl amine*, distilled as a yellow liquid, b.p. 110–114° (0.1 mm.), 6.0 g. (54%). Attempted redistillation led to polymerization and/or decomposition. A *picrate* derivative separated from 95% ethanol as yellow needles and was further purified by recrystallization from ethyl acetate and hexane mixtures. A sample, m.p. 181–182° (dec.), was analyzed.

Anal. Calcd. for $C_{12}H_{12}N_2$;$C_6H_3N_3O_7$: C, 52.31; H, 3.66; N, 16.94. Calcd. for $C_{12}H_{12}N_2$;$C_6H_3N_3O_7$;$^1/_2H_2O$: C, 51.19; H, 3.82; N, 16.58. Found: C, 51.15; H, 3.63; N, 16.71.

Reduction of 2-benzoylpyridine by the Leuckart reaction. According to a general procedure of Crossley and More[12] for the Leuckart reaction, 35 g. (0.57 mole) of 28% ammonium hydroxide and 29.3 g. (0.57 mole) of 90% formic acid were added to a three-necked flask equipped with a dropping funnel, thermometer, and distilling condenser. As water was removed by distillation, the temperature was raised to 160° and 21.0 g. (0.115 mole) of 2-benzoylpyridine was added all at once. The mixture was held at 160–170° for 9 hr., cooled, treated with 40 ml. of concentrated hydrochloric acid, refluxed for 8 hr., cooled, diluted with 70 ml. of water, and extracted with benzene. The aqueous layer was treated with a little charcoal and made alkaline with concentrated ammonium hydroxide. An oil was extracted into benzene, washed with water, dried over sodium sulfate, and distilled. Benzene was removed at 1 atm. and 2.8 g. (12.6%) of a viscous yellow liquid, b.p. 168–174° (0.5 mm.) was obtained. It rapidly darkened upon standing. The structural assignment, 1-phenyl-2:3a-diazaindene was in agreement with elemental analyses of its picrate derivative, m.p. 209–212° (dec.) in a bath preheated to 204°. Blue fluorescence under ultraviolet light was reported for 2:3a-diazaindene[4] and was also observed for 1-phenyl-2:3a-diazaindene.

Anal. Calcd. for: $C_{13}H_{10}N_2 \cdot C_6H_3N_3O_7$: C, 53.90; H, 3.10; N, 16.55. Found: C, 54.14; H, 3.39; N, 16.56.

Preparation of amides. One ml. of benzoyl chloride was added dropwise to a solution of 1.0 g. (0.005 mole) of phenyl 2-pyridylmethyl amine in 10 ml. of dry pyridine and 20 ml. of dry benzene. The mixture was heated at 60–70° for 30 min., poured into 200 ml. of water, the aqueous layer separated and washed with benzene. The combined benzene layer and washings were washed with 20 ml. of water and 20 ml. of 5% sodium carbonate solution, dried over anhydrous sodium sulfate, concentrated to 10 ml., and added to 20 ml. of hexane whereupon *N-benzoyl phenyl(2-pyridyl)methyl amine* separated as colorless needles, m.p. 124–125°, 0.76 g. (49%), and was recrystallized from aqueous ethanol.

Anal. Calcd. for $C_{19}H_{16}N_2O$: C, 79.13; H, 5.59; N, 9.92; O, 5.55. Found: C, 79.25; H, 5.65; N, 9.91; O, 5.47.

N-p-nitrobenzoyl 2-pyridylmethyl amine, m.p. 135–137°,[13] was prepared in a similar manner from 2-pyridylmethyl amine and *p*-nitrobenzoyl chloride.

N-nitrosoamides. To a solution of 0.85 g. (0.003 mole) of N-*p*-nitrobenzoyl 2-pyridylmethyl amine in 3 ml. of acetic acid and 17 ml. of acetic anhydride cooled to 0°, 5.0 g. (0.07 mole) of sodium nitrite was added over a period of 4 hr. The mixture was then kept at 0° for 10 hr., poured into ice water, and extracted with ether. The ether layer was washed with water, 5% sodium bicarbonate, again with water, and dried over anhydrous sodium sulfate. Upon removal of solvent *in vacuo*, an unstable orange oil, assumed to be *N-2-picolyl-N-nitroso-p-nitrobenzamide*, was dissolved in 30 ml. of toluene and heated at 100–110° for 5 hr. The mixture was extracted with 5% sodium bicarbonate solution, and then with 5% hydrochloric acid. Upon neutralization of the combined acid extracts crude *2-pyridylmethyl p-nitrobenzoate* precipitated. It recrystallized from ethanol as colorless needles, 0.17 g. (20% based on N-*p*-nitrobenzoyl 2-pyridylmethyl amine), m.p. and mixture m.p. 90–92°.[14]

In attempts to nitrosate *N*-benzoyl phenyl(2-pyridyl)-methyl amine with nitrogen tetroxide or with isoamyl nitrite starting material was quantitatively recovered. Impure unidentified products were obtained upon all attempts to combine nitrous acid and either phenyl 2-pyridylmethylamine or 2-pyridylmethylamine in aqueous media. An unidentified yellow liquid, b.p. 94–98° (3.2 mm.), was obtained from 2-pyridylmethyl amine and isoamyl nitrite in glacial acetic acid. It solidified upon standing and then decomposed into a dark oil. A picrate derivative after repeated recrystallizations had a melting range 155–163°.

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(7) Semi-micro analyses by Alfred Bernhardt, Microanalytisches Laboratorium, Mülheim (Ruhr), Germany.

(8) E. H. Huntress and H. C. Walter, *J. Am. Chem. Soc.*, **70**, 3702 (1948) reported m.p. 116–145°.

(9) H. G. Kolloff and J. H. Hunter, *J. Am. Chem. Soc.*, **63**, 490 (1941).

(10) R. Mozingo, D. E. Wolf, S. A. Harris, and K. Folkers, *J. Am. Chem. Soc.*, **65**, 1013 (1943).

(11) A b.p. 81° (12 mm.) for a sample from the reduction of α-cyanopyridine with lithium aluminum hydride was reported.[1]

(12) F. S. Crossley and M. L. More, *J. Org. Chem.*, **9**, 529 (1944).

(13) R. Graf, G. Perathoner, and M. Tatzel, *J. prakt. Chem.*, **146**, 88 (1936) reported 136°.

(14) The ester was identical with the product obtained from *p*-nitrobenzoic acid and pyridotriazole [J. H. Boyer and L. T. Wolford, *J. Am. Chem. Soc.*, **80**, 2741 (1958)].

Hydrogenation of Thiophene Compounds with Hydrogen and Carbon Monoxide and a Cobalt Catalyst

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Received December 9, 1957

Previous attempts to hydrogenate the thiophene nucleus to thiolane have been only partly successful.[4] Thiophenes have been reduced to thiolanes over a palladium catalyst, but very large quantities of catalyst were required to overcome the poisoning effect.[5] Alkyl derivatives of thiophene and thiolane

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(2) Bureau of Mines, Region V, U. S. Department of the Interior, Pittsburgh, Pa.

(3) Department of Chemistry, University of Cincinnati, Cincinnati 21, Ohio.

(4) H. D. Hartough, *Thiophene and Its Derivatives*, Interscience Publishers, Inc., New York, 1952, p. 167.

(5) R. Mozingo, S. A. Harris, D. E. Wolf, C. E. Hoffhine, Jr., N. R. Easton, and K. Folkers, *J. Am. Chem. Soc.*, **67**, 2092 (1945).

TABLE I

REDUCTION OF THIOPHENE COMPOUNDS WITH SYNTHESIS GAS ($2H_2$:1CO)[a] AND A COBALT CATALYST[b] AT 180–190°

Starting Compound	Moles of Starting Compound	Benzene, Ml.	Weight of Cobalt, g.	Time, Hr.	Products	
					Composition	% yield
Thiophene	1.15	20	6	5	Thiophene	25
					Thiolane[c]	50
Thiophene	1.01	80	10	4	Thiophene[d]	24
					Thiolane[d]	66
2-Methylthiophene	0.89	20	1.4	4	2-Methylthiophene	39
					2-Methylthiolane[e,f]	51
2-Methylthiophene	1.00	80	2.6	5[g]	2-Methylthiophene[d]	5
					2-Methylthiolane[d]	77
2-Ethylthiophene	0.40	80	2.6	3	2-Ethylthiophene[d]	6
					2-Ethylthiolane[d]	82
2,5-Dimethylthiophene	0.44	50	1.4	5	2,5-Dimethylthiophene[h]	53
					2,5-Dimethylthiolane[h]	22
2-Thenyl alcohol	0.36	50	1.4	4	2-Methylthiophene	24
					2-Methylthiolane[f]	57
2-Acetylthiophene	0.72	20	2.7	9[i]	2-Ethylthiophene	52
					2-Ethylthiolane	26

[a] Initial pressure of 3500–4000 p.s.i. at room temperature. [b] Dicobalt octacarbonyl or a mixture of dicobalt octacarbonyl and cobaltous carbonate. [c] Mercuric chloride addition product melted at 130.1–131.0° and did not depress melting point of an authentic sample; reported melting point, 129–130°.[5] [d] Identified and analyzed by mass spectrometry. [e] Identified by mass spectrometry. Mercuric chloride addition product melted at 160.3–161.0° after recrystallization from ethanol; reported melting point, 162°.[17] [f] n_D^{25} 1.4880; reported value, 1.4884.[17] [g] After pressure dropped to 3200 p.s.i. in 4 hr., autoclave was repressured to 4000 p.s.i. at 190°. [h] Yields estimated from boiling point–refractive index curve of mixture. Geometric configuration of 2,5-dimethylthiolane not determined. [i] After pressure dropped to 3000 p.s.i. in 4 hr., autoclave was cooled and repressured to 3500 p.s.i. at room temperature.

have been obtained by hydrogenation of 2-acylthiophenes in the presence of sulfur and cobalt polysulfide;[6] however, thiophene and 2-methylthiophene were not reduced by this method. Thiophene has been hydrogenated to thiolane with a molybdenum sulfide catalyst, but in low yield.[7–10] Rhenium heptasulfide is reported to be a satisfactory catalyst for the hydrogenation of thiophene to thiolane[10] and merits further investigation.

Earlier work in this laboratory had shown that a cobalt catalyst and synthesis gas (a mixture of hydrogen and carbon monoxide) may be used to reduce 2-thiophenecarboxaldehyde to 2-thenyl alcohol and 2-methylthiophene;[11,12] 2-acetylthiophene to 2-ethylthiophene;[12,13] and thiophene to thiolane in low yield.[13]

It has now been found that thiophene can be reduced to thiolane and that alkylthiophenes, 2-thenyl alcohol, and 2-acetylthiophene, can be reduced to the corresponding alkylthiolanes at 180° to 190° by using longer reaction times with excess synthesis gas and larger amounts of cobalt catalysts. The yields are high enough for the reaction to be of preparative interest. These hydrogenations are probably homogeneously catalyzed by cobalt carbonyl and/or cobalt hydrocarbonyl.[14,15]

In general the reduction of substituted thiophenes proceeded more readily than that of thiophene itself, and it was not difficult to obtain good yields of substituted thiolanes. That the hydrogenation of thiophene to thiolane was not reversible was demonstrated by treating thiolane with cobalt carbonyl and synthesis gas at 180° to 190°; mass spectrometric analysis of the products showed that no thiophene had been formed under these conditions. Attempts (not reported herein) to increase the yield of thiolane by employing even larger amounts of catalyst with very long reaction times and repressuring with fresh synthesis gas were not successful. Desulfurization occurred and the catalyst was partly converted to cobalt sulfide and metallic cobalt, as shown by x-ray diffraction analysis. It is possible that higher partial pressures of carbon monoxide would have preserved the catalyst as cobalt carbonyl.

(6) E. Campaigne and J. L. Diedrich, *J. Am. Chem. Soc.*, **73**, 5240 (1951).

(7) B. L. Moldavskii and N. Prokopchuk, *J. Appl. Chem. (U.S.S.R.)*, **5**, 619 (1932).

(8) B. L. Moldavskii and Z. I. Kumari, *J. Gen. Chem. (U.S.S.R.)*, **4**, 298 (1934).

(9) C. M. Cawley and C. C. Hall, *J. Soc. Chem. Ind. (London)*, **62**, 116 (1943).

(10) H. S. Broadbent, L. H. Slaugh, and N. L. Jarvis, *J. Am. Chem. Soc.*, **76**, 1519 (1954).

(11) I. Wender, R. Levine, and M. Orchin, *J. Am. Chem. Soc.*, **72**, 4375 (1950).

(12) I. Wender and M. Orchin, U. S. Patent **2,587,671** (1952).

(13) I. Wender, H. Greenfield, and M. Orchin, *J. Am. Chem. Soc.*, **73**, 2656 (1951).

(14) I. Wender, M. Orchin, and H. H. Storch, *J. Am. Chem. Soc.*, **72**, 4842 (1950).

(15) M. Orchin, *Advances in Catalysis*, Vol. V, Academic Press, Inc., New York, 1953 pp., 385–415.

EXPERIMENTAL

Melting points are corrected.

Synthesis gas (a mixture of hydrogen and carbon monoxide) was manufactured and compressed by the Bureau of Mines at Bruceton, Pa. Dicobalt octacarbonyl[13] and 2-ethylthiophene[16] were prepared by methods described in the literature. 2-Acetylthiophene was obtained from commercial sources. Thiophene, 2-methylthiophene, and 2,5-dimethylthiophene were gifts of the Socony-Vacuum Oil Co. 2-Thenyl alcohol was prepared in 85% yield by the lithium aluminum hydride reduction of 2-thiophenecarboxaldehyde in refluxing ethyl ether.

Each experiment was conducted at 180–190° with an initial pressure of 3500–4000 p.s.i. of 2:1 synthesis gas ($2H_2$:1CO) at room temperature, using benzene as solvent and dicobalt octacarbonyl, or a mixture of dicobalt octacarbonyl and cobaltous carbonate, as catalyst in a 500-ml., type 347 stainless steel, rocking autoclave purchased from the American Instrument Co. A 2-foot Heligrid Podbielniak column was used for precision fractional distillations.

The results are shown in Table I. A detailed description of the reduction of 2-acetylthiophene is given as an example.

Reduction of 2-acetylthiophene. In the 500-ml. autoclave were placed 90.0 g. (0.72 mole) of 2-acetylthiophene, 3.0 g. of cobaltous carbonate, and 20 ml. of a benzene solution containing 1.3 g. of dicobalt octacarbonyl. The autoclave was pressured to 3500 p.s.i. with 2:1 synthesis gas at room temperature and heated at about 185°. After the pressure had dropped to 3000 p.s.i. in 4 hr., the autoclave was cooled to room temperature and repressured from 1700 to 3500 p.s.i. It was then heated at about 185° for an additional 5 hr. The final pressure at room temperature was 3100 p.s.i. A total of 2.6 moles of gas had been absorbed. Fractional distillation of the reaction mixture gave 41.7 g. (52%) of 2-ethylthiophene, b.p. 133–135°, and 21.7 g. (26%) of 2-ethylthiolane, b.p. 154–158°. After purification by chromatographic absorption through silica gel, followed by azeotropic distillation with Cellosolve, the 2-ethylthiolane had the following physical constants: b.p. 156° at 736 mm., n_D^{25} 1.4870, d_D^{20} 0.9405.

Anal. Calcd. for $C_6H_{12}S$: C, 62.00; H, 10.41. Found: C, 62.08; H, 10.42.

Acknowledgment. We are indebted to Andrew G. Sharkey, Jr., for the spectroscopic analyses; to L. J. E. Hofer for the x-ray diffraction analyses, and to Walter Rosinski for the macroanalyses.

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(16) W. J. King and F. F. Nord, *J. Org. Chem.*, **14**, 638 (1949).

(17) E. V. Whitehead, R. A. Dean, and F. A. Fidler, *J. Am. Chem. Soc.*, **73**, 3632 (1951).

An Anomalous Reaction of Michler's Ketone with Grignard Reagents

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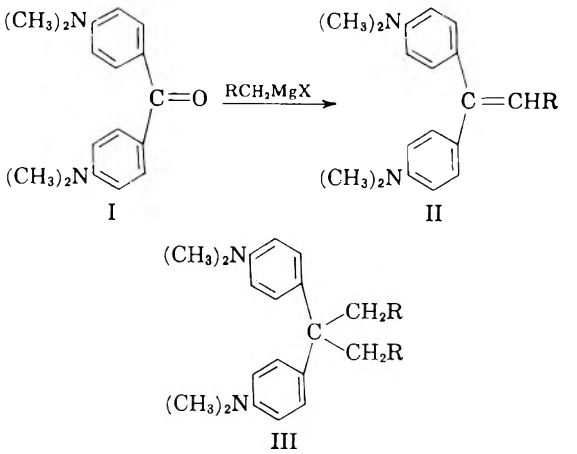
Received December 18, 1958

The reaction of Michler's ketone (I) with Grignard reagents to give the corresponding di- or triphenylmethane dyes is the basis for a very sensitive color test for Grignard reagents.[1] As a preparative tool, however, this reaction is often unsatisfactory and wide variations in yields of the corresponding 1,1-bis(*p*-dimethylaminophenyl)ethylenes have been reported.[2]

Roleff[2f] reported quantitative yields of II(R = H) when Michler's ketone was heated with four moles of methylmagnesium bromide in benzene. Repetition of his procedure furnished 40–50% of 2,2-bis(*p*-dimethylaminophenyl)propane (III, R = H) in addition to II. Under similar conditions, benzylmagnesium chloride and I gave an 80% yield of III(R = C_6H_5 or the *o*-tolyl isomer) and no detectable II(R = C_6H_5).

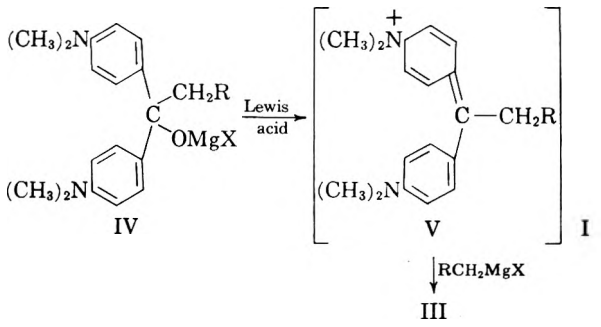


Although this anomalous reaction of Grignard reagents with Michler's ketone to form the corresponding dialkyl compounds has not been described, several examples of similar reactions of Grignard reagents with carbonyl compounds have been reported.[3] In all examples, an amino nitrogen is adjacent to or conjugated with the carbonyl group. This suggests that the reaction proceeds through a resonance-stabilized carbonium ion. Thus, the intermediate IV may be converted to V by a process in which a molecule of Grignard reagent, or the magnesium halide in equilibrium with the Grignard reagent, functions as a Lewis acid. The ion V then reacts with more Grignard to give the product III.

(1) H. Gilman and F. Schulze, *J. Am. Chem. Soc.*, **47**, 2002 (1925).

(2) (a) H. Fecht, *Ber.*, **40**, 3902 (1907); (b) G. Busignies, *Compt. rend.*, **149**, 349 (1909); (c) M. Freund and F. Mayer, *Ber.*, **39**, 1117 (1906); (d) P. Pfeiffer and R. Wizinger, *Ann.*, **461**, 132 (1928); (e) D. S. Tarbell and E. G. Lindstrom, *J. Am. Chem. Soc.*, **68**, 1930 (1946); (f) Roleff, *Chem. Ztg.*, **67**, 81 (1943); *Chem. Abstr.*, **38**, 5207.

(3) (a) F. Sachs and W. Weigert, *Ber.*, **40**, 4361 (1907); W. L. Semon and D. Craig, *J. Am. Chem. Soc.*, **58**, 1278 (1936); R. Lukes and O. Frossman, *Collection Czechoslov. Chem. Commun.*, **8**, 533 (1936).



A very similar mechanism has been proposed by Conover and Tarbell[4] for the hydrogenolysis of some amino- and alkoxy-substituted aromatic acids and carbonyl compounds by lithium aluminuim hydride. The reaction was only observed with those compounds which are capable of forming a carbonium ion highly stabilized by resonance.

In agreement with this hypothesis, the reaction of *p*-dimethylaminobenzophenone with a large excess of methylmagnesium bromide in boiling benzene did not afford a detectable quantity of anomalous product corresponding to III.

EXPERIMENTAL

Reaction of Michler's ketone with methylmagnesium bromide. A suspension of 2.0 moles of methylmagnesium bromide in 500 ml. of benzene under nitrogen was treated with 128 g. (0.48 mole) of Michler's ketone, m.p. 173–176°, dissolved in 1.5 liters of hot benzene. After heating under reflux for 3 hr., the mixture was chilled and treated with saturated ammonium chloride solution. The crude product (119 g.), m.p. 60–110°, was fractionally crystallized from ethanol to give 59 g. (46.5%) of II, R = H, m.p. 122–124° (lit. m.p. 124°). The balance of the material was obtained as crude III, R = H, m.p. 60–75°. Repeated recrystallization of the latter from aqueous alcohol afforded material melting at 78.5–81°.

Anal. Calcd. for $C_{19}H_{26}N_2$: C, 80.80; H, 9.28; N, 9.92. Found: C, 80.49; 80.60; H, 9.58, 9.62; N, 10.06, 9.90.

An authentic sample of III, R = H, m.p. 80–83.5°, mixed m.p. 78.5–82°, was prepared by the reaction of dimethylaniline hydrochloride with acetone.[5] The infrared spectra of the two samples were identical.

Reaction of Michler's ketone with benzylmagnesium chloride. A suspension of 0.8 mole of benzylmagnesium chloride[6] in 150 ml. of benzene under nitrogen was treated with 52.5 g. (0.20 mole) of Michler's ketone dissolved in 400 ml. of boiling benzene. The mixture was heated under reflux for 5 hr., then chilled and treated with saturated ammonium chloride. The crude product was washed twice with warm ethanol to give 70 g. (80.5%) of white solid, m.p. 165–173°. This dissolved readily in dilute hydrochloric acid to give a colorless solution, showing the absence of II (R = C_6H_5) or the corresponding carbinol. Both of these compounds would give intense blue or green colors with dilute acids. An analytical sample, m.p. 169–173°, was prepared by recrystallization from ligroin (Skellysolve B).

Anal. Calcd. for $C_{31}H_{34}N_2$: C, 85.67; H, 7.89; N, 6.45. Found: C, 85.73, 85.97; H, 8.03, 7.92; N, 6.83, 6.72.

Heating of the material at 60° for several days caused a progressive lowering of the melting point, apparently due to rearrangement since the composition was unchanged. The reaction product of benzylmagnesium chloride with 1,2,3,4-tetraphenylfulvene undergoes a similar depression of the melting point on standing.[7]

An attempt to prepare III (R = C_6H_5) by the reaction of dimethylaniline hydrochloride with dibenzyl ketone at 170° resulted in nearly complete recovery of starting materials.

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(4) L. H. Conover and D. S. Tarbell, *J. Am. Chem. Soc.*, **72**, 3586 (1950).

(5) J. von Braun, *Ann.*, **472**, 1 (1929).

(6) H. Gilman and W. E. Catlin, *Org. Syntheses*, Coll. Vol. I, 471 (1941).

(7) A. G. Bonagura, M. B. Meyers, J. J. Storfer, and E. I. Becker, *J. Am. Chem. Soc.*, **76**, 6122 (1954).

Reaction of 1-Bromo-2,3-epoxybutane and 3-Bromo-1,2-epoxybutane with Phenol[1]

RICHARD L. ROWTON AND ROBERT R. RUSSELL

Received December 20, 1957

The reaction between epichlorohydrin and phenol in basic solution has been reported by Boyd and Marle[2] as producing 3-phenoxy-1,2-epoxypropane. This result leads to some interesting speculations as to the mechanism of the reaction. Because of the structure of the epichlorohydrin, it is impossible to state beyond peradventure whether the phenoxide ion reacted by a simple replacement of the chloride ion from the epichlorohydrin, or whether the phenoxide ion first attacked the terminal epoxide carbon to form an intermediate secondary alkoxide ion which became stabilized by loss of the chloride ion and formation of a new oxirane ring. The final product in either case would be the same. An interesting point of conjecture is the lack of reaction between the phenoxide ion and the central carbon of the epichlorohydrin. From considerations of the electronic structure of the molecule one would expect this central carbon atom to be the most highly electrophilic,[3] hence in the absence of other influences predominate reaction should be at this carbon.

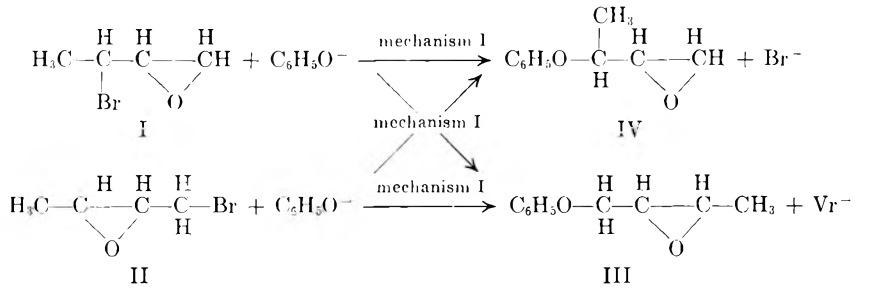
To obviate the difficulty inherent in the structure of epichlorohydrin in studying this reaction mechanism, two isomeric haloepoxides were used which are similar in structure to epichlorohydrin. These compounds were 3-bromo-1,2-epoxybutane, I, and

(1) This paper was presented before the Organic Division of the American Chemical Society at its 125th meeting in Kansas City, Mo., March 23 to April 1, 1954.

(2) D. R. Boyd and E. R. Marle, *J. Chem. Soc.*, **93**, 838 (1908).

(3) The chloromethyl group tends to withdraw electrons in one direction from this carbon and the oxygen atom in the other. See A. E. Remick, *Electronic Interpretations of Organic Chemistry*, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 59.

1-bromo-2,3-epoxybutane, II.[4] If direct replacement of bromine in each compound is designated as *mechanism one* and initial attack of the phenoxide ion on the epoxide carbon farthest from the halogen bearing carbon is designated *mechanism two*, the two possibilities can be represented by the following reactions.



In the reactions representing mechanism two it is understood that a secondary alkoxide ion is formed as an intermediate[5] which becomes stabilized by loss of a bromide ion.

Identification of the products of reaction was accomplished by oxidation of the phenoxy substituted epoxides with silver oxide in the presence of 10% sodium hydroxide solution. The products of oxidation thus produced were acids which were identified by melting points and melting points of their derivatives.

The products of reaction here reported indicate that in both cases the phenoxide ion reacted with the bromoepoxides by initial attack on the epoxide carbon atom remote from the halogen bearing carbon atom and that reaction thus occurred *via* mechanism II. It is interesting to note that in the reaction of the same two epoxides with the methoxide ion in methanol and the ethoxide ion in ethanol, reported by Waters and VanderWerf,[5i] a single mechanism does not obtain. In these reactions the terminal epoxide I reacted by mechanism II whereas the internal epoxide II reacted according to what we have termed mechanism I.

EXPERIMENTAL

Reaction of 3-bromo-1,2-epoxybutane, I, *with phenol*. In a typical reaction, 28 g. (0.185 mole) of I was stirred with 17.4 g. (0.185 mole) of phenol and 9.3 g. (0.23 mole) of sodium hydroxide in 110 ml. of water at 25° for 20 hr. The organic layer was then separated and combined with the ether extract of the aqueous layer. After drying over anhydrous sodium sulfate, the ether was removed and the residual material was vacuum distilled to yield 10.5 g. of recovered I, a small intermediate fraction, and 10 g. of 1-phenoxy-2,3-epoxybutane, III, b.p. 111–116° at 5 mm. 53% of the theoretical yield based upon I not recovered.

Anal. Calcd. for $C_{10}H_{12}O_2$: C, 73.14; H, 7.43; oxirane oxygen,[6] 9.64 Found: C, 72.28; H, 7.17; oxirane oxygen, 9.59.

Reaction of 1-bromo-2,3-epoxybutane, II, *with phenol*. In an analogous procedure to the above, 0.432 mole of II, 0.432 mole of phenol, 0.54 mole of sodium hydroxide in 260 ml. of water, were stirred for 12 hr. at 25°. The organic layer and the ether extract of the aqueous layer were dried over sodium sulfate as before. The residue after removal of the ether was vacuum distilled to give 7.3 g. of 3-phenoxy-1,2-epoxybutane, IV, b.p. 105–108° at 5 mm., 32% based on II not recovered.

Anal. Calcd. for $C_{10}H_{12}O_2$: C, 73.14; H, 7.43; oxirane oxygen, 9.64. Found: C, 73.27; H, 7.27; oxirane oxygen, 9.40.

Oxidation of 1-phenoxy-2,3-epoxybutane, III. Oxidation of III was carried out by stirring 1 g. with 5 g. of silver oxide and 50 ml. of 10% sodium hydroxide solution for 24 hr. on the steam bath. At the end of this time the aqueous layer was separated by filtration, acidified, then extracted with ether, dried, and ether evaporated. The white crystalline residue was recrystallized twice from hot water and 0.15 g. of pure phenoxyacetic acid, m.p. 97–98°, was recovered. The *p*-bromophenacyl ester was prepared and melted at 149–151°. There was no depression in mixed melting points with authentic samples. No other acid was isolated from the reactions.

Oxidation of 3-phenoxy-1,2-epoxybutane, IV. The oxidation of IV was carried out in exactly the same manner as with III. The same quantities of material were used. The material was filtered and the filtrate acidified with dilute hydrochloric acid to precipitate a white crystalline solid. This solid was separated and recrystallized from hot water to yield 0.6 g. of 2-phenoxypropionic acid, m.p. 114.5–116°. A small additional quantity was obtained from ether extraction of the aqueous mother liquor. No other acid was found, however. The amide and the *p*-toluidide were prepared and found to melt at 129–130° and 114–115°, respectively. These values are in good agreement with the literature values for 2-phenoxypropionic acid and derivatives.

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(4) These compounds were prepared from crotyl bromide by the method of Petrov. A. A. Petrov, *J. Gen. Chem.* (*U.S.S.R.*), **11**, 713 (1941). No attempt was made to separate the stereoisomers of II reported by Petrov.

(5) Numerous examples of this behavior of epoxides in basic solution have been reported: (a) S. J. Cristol and R. G. Helmreich, *J. Am. Chem. Soc.*, **74**, 4083 (1952). (b) G. K. Helmkamp and H. J. Lucas, *J. Am. Chem. Soc.*, **74**, 951 (1952). (c) C. O. Guss, *J. Am. Chem. Soc.*, **71**, 3460 (1949). (d) W. Reeve and A. Sadle, *J. Am. Chem. Soc.*, **72**, 1251 (1950). (e) R. M. Adams and C. A. VanderWerf, *J. Am. Chem. Soc.*, **72**, 4368 (1950). (f) R. R. Russell and C. A. VanderWerf, *J. Am. Chem. Soc.*, **69**, 11 (1947). (g) H. E. Chitwood and B. T. Freure, *J. Am. Chem. Soc.*, **68**, 680 (1946). (h) R. G. Kadesch, *J. Am. Chem. Soc.*, **68**, 41 (1946). (i) R. C. Waters and C. A. VanderWerf, *J. Am. Chem. Soc.*, **76**, 709 (1954).

(6) The method of Swern *et al.* was used to determine oxirane oxygen. Daniel Swern, T. W. Finley, G. H. Billen, and J. T. Scanlan, *Ind. Eng. Chem., Anal. Ed.*, **19**, 414 (1947).

An Oxidation-Reduction Reaction Involving Triphenylcarbinol

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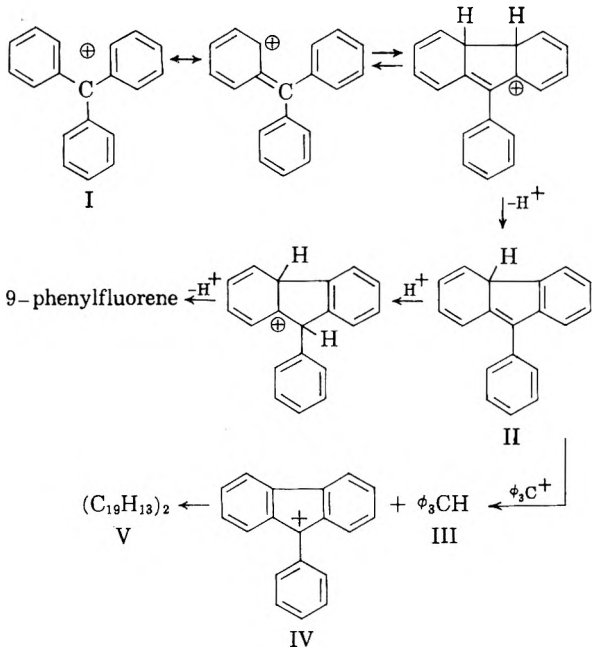
Received December 23, 1957

The recent report[1] that a 90% yield of triphenylmethane can be realized by heating a solution of triphenylcarbinol with sulfuric and glacial acetic acids was of considerable interest to us. The uncertainty expressed[1] as to the path of this reaction is indeed justified when one considers that the excellent yield of triphenylmethane reported is evidence for a reduction in the absence of any conceivable reducing agent.

We therefore undertook a reinvestigation of this reaction and found that contrary to the original report, the product is a mixture of at least *three* different hydrocarbons. Chromatographic separation of the crude product afforded triphenylmethane, 9-phenylfluorene and an unidentified amorphous hydrocarbon with an approximate formula of $(C_{19}H_{13})_2$.

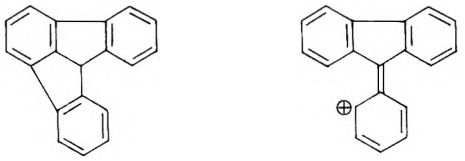
Although it is apparent that reduction is indeed taking place, the isolation of these products allows a rational picture for the over-all process:



The triphenylcarbonium ion (I) generated in the strongly acid medium can rearrange in an *intra*molecular oxidation-reduction, to form 9-phenylfluorene from intermediate II as shown above. Intermediate II could also participate in an *inter*molecular process whereby a hydride ion is transferred to the triphenylcarbonium ion, in what would probably be a concerted process, to form triphenylmethane III and a new carbonium ion IV. This new carbonium ion then can proceed to give the third hydrocarbon V whose structure is problematical. The infrared spectrum of V was complex and indicated that it may well be a mixture, but there was an over-all similarity to the spectrum of hydrindene.[2]

Cryoscopic molecular weight determinations of V gave an average value in the vicinity of 500, possibly indicating some type of dimeric structure of 9-phenylfluorene. Such a structure could conceivably arise by the intermolecular attack of IV on another molecule of 9-phenylfluorene. Such an attack would probably result in a mixture consisting of several closely related isomeric structures, which would account for the difficulties encountered in the purification of this material.

At first it was thought that V might be the strained hydrocarbon indeno[1.2.3-*jk*]fluorene (VI). Such a compound could conceivably arise from



ion VII in a manner analogous to the formation of 9-phenylfluorene. However the molecular weight obtained for V, together with the isolation of a small amount of benzoic acid from the chromic acid oxidation of this material would argue against the presence of any of VI in the mixture.

Confirmatory evidence for the formation of carbonium ion IV can be obtained from earlier work by Kovache[3] who treated 9-phenyl-9-hydroxyfluorene with hot formic acid. Although the product was not adequately characterized it was reported as as amorphour material with solubility characteristics similar to those of V and with a melting range (165–170°) which corresponded closely to that of our material before purification.[4]

EXPERIMENTAL

A mixture of 2.6 g. (.01 mole) of triphenylcarbinol, 5 ml. of concentrated sulfuric acid, and 30 ml. of glacial acetic acid was heated to reflux. The carbinol dissolved to give a deep yellow-orange solution which began to deposit an oil after a few moments. After refluxing for 2 hr. the orange-brown mixture was cooled and the liquid was decanted from a heavy yellow gum.

The gum was taken up in benzene and this solution washed with base and water and dried over magnesium sulfate.

(1) C. A. MacKenzie and G. Chuchani, *J. Org. Chem.*, 20, 342 (1955).

(2) Infrared Spectral Data—American Petroleum Institute Research Project 44. Spectrum 1147.

(3) A. Kovache, *Ann. chim. (Paris)* [9], 10, 206 (1918).

(4) It should also be noted that Schorigin [*Ber.*, 60, 2375 (1927)] also observed the formation of triphenylmethane in low yield from triphenylcarbinol. While he conjectured that oxidation products like 9-phenylfluorene might also be formed, he did not characterize such products.

After removing most of the solvent on the steam plate, the solution was poured onto an alumina column (Merck). Development and elution with 15% benzene in petroleum ether (60–70°) gave 2 fractions which were subsequently recrystallized from ethanol. The first afforded 400 mg. (17%) of triphenylmethane melting at 92° and not depressed by an authentic sample. The second gave 210 mg. of 9-phenylfluorene melting at 147–148° and not depressed by an authentic sample.[5]

Elution of the column with benzene gave a colorless gum which solidified on treatment with ethanol. The yield of material melting at 160–180° was 700 mg. After several reprecipitations from benzene with ethanol, the melting point of this white amorphous solid was 200–203°. Further efforts at purification or crystallization were fruitless. The material was soluble in all of the common organic solvents except alcohols and acetic acid. It did not dissolve in concentrated sulfuric acid. Oxidation of 900 mg. of the hydrocarbon with chromic acid in acetic acid afforded a few milligrams of benzoic acid melting at 121–122° and undepressed by admixture with an authentic sample.

Anal., Calcd. for $(C_{19}H_{13})_2$: C, 94.6; H, 5.4. Found: C, 95.03; H, 5.2.

Three cryoscopic molecular weight determinations of V in benzene gave values of 510, 498, and 530. Calcd. for $(C_{19}H_{13})_2$: mol. wt., 482.6.

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(5) A. Kliegl, *Ber.*, **38**, 287 (1905).

4-(4-Aminostyryl)quinolines[1]

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Received December 23, 1957

A series of analogs of 4-(4-dimethylaminostyryl)-quinoline (I)[2,3] have been prepared in which other groups have the place of the dimethylamino group. 4-(4-Aminostyryl)quinoline, prepared by two different methods, was a convenient intermediate for the preparation of a variety of derivatives through reactions of the primary amino group. The effectiveness of oral administration of the compounds in causing regression or inhibition of growth of Lymphoma 8 tumors in rats is being tested at the Wistar Institute of Anatomy and Biology through the cooperation of Dr. Margaret Reed Lewis, Dr. Boland Hughes, and Mr. Aubrey L. Bates, and the financial assistance of a grant-in-aid from the National Institutes of Health. Effectiveness of intraperitoneal injection of arachis oil solutions of the compounds in preventing growth of Walker 256 tumors is being tested by Professor Alexander Haddow and his associates at the Chester Beatty Research Institute. Most of the compounds reported here were less active than I against the tumors, in that larger doses were necessary in order to produce a given response, but the toxic side effects varied with the compound and method of administration. Some of the compounds had the advantage of being much less toxic than I. A more detailed report of the biological observations is to be made elsewhere.

EXPERIMENTAL

4-(4-Diethylaminostyryl)quinoline (II) did not crystallize as readily as I from the still residue obtained by the general method of Clapp and Tipson.[3] Isolation of the product through the zinc salt[4] was more convenient. II was found to be as active as I against Lymphoma 8.[5] The hydrochloride, administered intravenously to leukemic rats, was reported to produce a prompt return of the white blood cell count to normal.[6]

4-(4-Diethylaminostyryl)-3-methylquinoline. Fifty-six grams (0.376 mole) of *p*-diethylaminobenzaldehyde was added to a molten mixture of 10.65 g. (0.078 mole) of zinc chloride and 25 g. of 3-methyllepidine (0.159 mole). After heating 8 hr. in an oil bath at 175–180°, the tarry reaction mixture was dissolved partially in methanol. Red crystals weighing 13.9 g. were separated from the solution. These were ground thoroughly with two portions of ammonium hydroxide, and washed with water. The tar thus produced was dissolved in hot isohexane. The yellow solution was decanted from the red oil that separated on cooling slightly. Cooling the solution to room temperature then precipitated 2.3 g. of solid which was recrystallized from 65 ml. of isohexane to yield 1.9 g., (4%) of yellow crystals, m.p. 104.6–107.1°.[7]

Anal. Calcd. for $C_{22}H_{24}N_2$: C, 83.50, H, 7.65. Found: C, 83.66, 83.60; H, 7.72, 7.56.[8]

The *picrate* of this base was obtained as dark red crystals; m.p. 270.0–270.8°.

Anal. Calcd. for $C_{28}H_{27}N_5O_7$: C, 58.10, H, 3.60, N, 14.73. Found: C, 58.33, 57.89; H 3.47, 3.75.[8]

4-[4-(N-Ethyl-N-methylamino)styryl]quinoline. By the method of Leese[9] a mixture of 27.3 g. (0.21 mole) 4-(*N*-ethyl-*N*-methylamino)benzaldehyde and 30 g. (0.21 mole) of lepidine hydrochloride was heated 30 min. in an oil bath at 150°. The dark purple mass solidified on cooling, and was dissolved in 400 ml. of hot methanol; then 200 ml. of distilled water and 100 ml. of concentrated ammonium hydroxide were added. The yellow-brown crystals that appeared on chilling were triturated with ammonium hydroxide in a mortar, washed with water, and dried; weight, 42.3 g., m.p. 96–99°; after 8 additional recrystallizations from methanol, m.p. 123.7–124.8°, yield 4.4 g. (8.7%).

Anal. Calcd. for $C_{20}H_{20}N_2$: C, 83.29, H, 6.99. Found: C, 83.27, 83.44, H, 6.97, 7.17.

4-[4-(N-Benzyl-N-ethylamino)styryl]quinoline. A mixture of 10 g. (0.07 mole) of lepidine, 16 g. (0.067 mole) of 4-(*N*-benzyl-*N*-ethylamino)benzaldehyde, and 4.8 g. of zinc chloride was heated 24 hr. at 110–120°. The reaction mixture was dissolved in chloroform, washed with ammonium hydroxide, and dried over sodium sulfate. The chloroform

(1) This research was aided by a grant from the American Cancer Society.

(2) H. Gilman and G. Karmas, *J. Am. Chem. Soc.*, **67**, 342 (1945).

(3) M. A. Clapp and R. S. Tipson, *J. Am. Chem. Soc.*, **68**, 1332 (1946).

(4) C. T. Bahner, Clarence Cook, John Dale, John Fain, Edgar Franklin, J. C. Goan, William Stump, and Joan Wilson, *J. Org. Chem.*, 22, 682 (1957).

(5) M. R. Lewis, B. Hughes, and A. L. Bates, *Growth*, **19**, 323 (1955).

(6) B. Hughes, M. R. Lewis, and A. L. Bates, *Nature*, **177**, 331 (1956).

(7) All melting points are corrected.

(8) Analyses by Weiler and Strauss.

(9) C. L. Leese, private communication.

was evaporated, leaving an oil. The oil was dissolved in absolute ethanol. Water was added and a tar separated. The liquid was decanted and the tar was dissolved in 75 ml. of absolute ethanol. After the solution had stood for two months, crystals formed and were filtered off. Six recrystallizations from ethanol and six recrystallizations from isohexane gave 1.9 g. (8%) of yellow crystals, m.p. 110.9–111.4°.

Anal. Calcd. for $C_{25}H_{24}N_2$: C, 85.68, H, 6.64. Found: C, 85.32, 85.49; H, 6.65, 6.72.[8]

4-[4-(N-Benzyl-N-ethylamino)styryl]quinoline methiodide. A solution of 1.00 g. of lepidine methiodide, 1.00 g. of 4-(*N*-benzyl-*N*-ethylamino)benzaldehyde, and 3 drops of piperidine in 75 ml. of methanol was boiled 1 hr. and filtered while hot. On chilling, the filtrate deposited dark purple crystals that were recrystallized five times from methanol; m.p. 189–190°, yield 0.31 g. (17%).

Anal. Calcd. for $C_{27}H_{27}N_2I$: C, 64.03; H, 5.37. Found: C, 64.10, 64.26; H, 5.11, 5.35.[8]

4-(4-Aminostyryl)quinoline. Twenty-six grams (0.094 mole) of 4-(4-nitrostyryl)quinoline was mixed with 120 ml. of hydrochloric acid to form a thin paste. This mixture was placed in a 500-ml. 3-necked flask equipped with a condenser and a sealed stirrer, and a solution of 182 g. of tin (II) chloride 2-hydrate in 100 ml. of hydrochloric acid was added. The mixture was refluxed, with stirring, for one hour. Cooling yielded yellow crystals. They were stirred with enough water to make a smooth paste; and then 800 ml. of 10% sodium hydroxide was added with mechanical stirring. The crystals were recovered by filtration, dried with warm air, extracted with isohexane in a Soxhlet extractor, and recrystallized three times from isopropyl alcohol and once from benzene to yield 15.3 g. of yellow crystals, m.p. 152.4–154.0°. Concentration of the mother liquors yielded another 1.5 g. of compound. The total yield was 16.8 g. (73%).

Anal. Calcd. for $C_{17}H_{14}N_2$: C, 82.90, H, 5.73. Found: C, 83.07, 82.76; H, 5.73, 5.77.[10]

This compound was prepared also from *p*-acetamidobenzaldehyde. Sixty-eight grams (0.5 mole) of zinc chloride and 143 g. (1 mole) of lepidine were mixed to form a white solid. Then 245 g. (1.5 mole) of *p*-acetamidobenzaldehyde was added and the mixture was heated at 180°, with frequent stirring until all the solid dissolved. At the end of 2.5 hr. lumps of red dough-like material were removed while hot. When they had cooled they were ground and then washed by boiling with one 400-ml. portion of methanol and two 500-ml. portions of methanol. The red residue, after drying in an oven, weighed 206 g. (58%). A 200-g. portion of this zinc salt was stirred for 40 min. with 1 liter of 7.5*N* ammonium hydroxide. The solid was separated by filtration, washed with water, and boiled 2 hr. with 1250 ml. of 4.8*N* hydrochloric acid. When all the solid had dissolved, the solution was heated another 15 min., allowed to cool to room temperature, and made basic with ammonium hydroxide. The yellow crystals which formed were filtered, washed with water, and dried in an oven at 100°. They were then extracted with one liter of benzene in a Soxhlet extractor; yield 75 g., m.p. 152–154°. They were shown to be genuine 4-(4-aminostyryl)quinoline by mixed melting point comparison with an analyzed sample made by reduction of 4-(4-nitrostyryl)quinoline. Reducing the volume of the mother liquor by distillation yielded successive batches weighing 18.5 g., m.p. 151.0–152.7°; 10 g., m.p. 151.6–153.3° and 2 g. The combined first and second methanol washings mentioned above were treated with 25 g. of zinc chloride in 50 ml. of methanol. A sticky mass separated which gradually changed into 114 g. of dark red crystals. There were treated in the same manner as the others to yield 17 g. of product, m.p. 150.7–152.4°. The total yield was 122.5 g. (50%).

4-(4-Formamidostyryl)quinoline. Twenty grams (0.0813 mole) of 4-(4-aminostyryl)quinoline and 200 ml. of 90% formic acid were refluxed for 40 min. The reaction mixture was cooled in an ice bath and stirred mechanically. The mixture was chilled 1 hr.; then it was filtered and the yellow crystals were washed with six 50-ml. portions of water. Three recrystallizations from methanol (15 ml./g.) gave yellow crystals that softened at 159° and melted at 162.5–164.1°, yield (85%).

Anal. Calcd. for $C_{18}H_{14}N_2O$: C, 78.81, H, 5.14. Found: C, 78.61, 78.71; H, 5.06, 5.17.[8]

N,N'-Bis[4-(4-quinolyl)styryl]formamidine. A solution of 12.0 g. (0.0488 mole) of 4-(4-aminostyryl)quinoline and 7.2 ml. of ethyl orthoformate in 140 ml. of absolute ethanol was refluxed 6 hr. This mixture was chilled 40 min. and filtered to yield 5.7 g. of yellow crystals. The mother liquor was allowed to stand for two days, after which filtration yielded another 1.35 g. of product. No more crystals were produced when the mother liquor was refluxed another 5.5 hr., but addition of 4 ml. of ethyl orthoformate, refluxing 3 hr., and standing overnight, yielded 3.5 g. more. Adding another 3 ml. of ethyl orthoformate to the mother liquor and refluxing 8 hr. gave no more compound. When the product proved only slightly soluble in hot ethyl acetate, alcohols, ether, and benzene, it was purified by extraction with benzene in a Soxhlet extractor. The benzene was filtered at room temperature and the crystals were dried 30 min. at 110°: yield 7.60 g., m.p. 224–225°, (softening at 220°).

Anal. Calcd. for $C_{35}H_{26}N_4$: C, 83.64, H, 5.21. Found: C, 83.55, 83.32; H, 5.13, 5.18.[8]

An additional 0.85 g. of the product was obtained from the mother liquors by concentrating and chilling them. Total yield 8.45 g. (69%).

4-(4-Carbamidostyryl)quinoline. Fifteen grams (0.0609 mole) of 4-(4-aminostyryl)quinoline was dissolved in 91 ml. of acetic acid, 60 ml. of water, and 2 ml. of hydrochloric acid. The solution was cooled in an ice bath, and 7.0 g. of potassium cyanate in 10 ml. of water was added. The solution was allowed to stand 45 hr.; then a small amount of precipitate was filtered from the solution and the filtrate was added dropwise to 150 ml. of ammonium hydroxide cooled by an ice bath and stirred mechanically. The yellow precipitate was filtered off and washed with four 75-ml. portions of water. The moist precipitate was boiled 30 min. with 600 ml. of benzene. The mixture was filtered hot, yielding 11.5 g. of brownish crystals and a yellow filtrate. The brownish crystals were recrystallized from a mixture of 200 ml. of ethanol and 500 ml. of benzene to yield 2.3 g. of pale yellow crystals. These were recrystallized by extraction with 300 ml. of benzene in a Soxhlet extractor, to yield 2.12 g. of white crystals (12%), m.p. 262–266° dec. (darkening from 220°).

Anal. Calcd. for $C_{18}H_{15}N_3O$: C, 74.72, H, 5.23. Found: C, 74.67, 74.67, 74.68; H, 5.24, 5.24, 5.28.[8]

4-[4-(Carbethoxyamino)styryl]quinoline. A solution of 10.0 g. (0.084 mole) of 4-(4-aminostyryl)quinoline and 8 ml. (0.084 mole) of ethyl chloroformate in 200 ml. of chloroform was refluxed 1.5 hr., then placed in the freezer. The 13.7 g. of reddish brown crystals were triturated with two successive 50-ml. portions of water. Filtration then yielded yellow crystals which, after drying for five days over Drierite, weighed 11.8 g. Six recrystallizations from benzene (25 ml./g. of compound), and drying 5 hr., at 100° at 0.4 mm, gave 7.0 g. (55%) of yellow crystals, m.p. 151.7–152.4°, (softens at 150.3°).

Anal. Calcd. for $C_{20}H_{18}N_2C_2$: C, 75.45, H, 5.70. Found: C, 75.50, 75.55; H, 5.75, 5.85.[10]

4-{4-[4-(Dimethylaminobenzal)amino]styryl}quinoline. Nine grams (0.0366 mole) of 4-(4-aminostyryl)quinoline and 5.49 g. (0.0368 mole) of *p*-dimethylaminobenzaldehyde were ground together in a mortar. The mixture was heated 1.5 hr. in an oven at 110°. The hard porous mass which formed was crushed to a powder and recrystallized from 1050 ml. of ethyl acetate. A second recrystallization from 900 ml. of ethyl acetate yielded 10.90 g. of light orange crystals, m.p. 194–195.5°.

(10) Analyses by Galbraith Laboratories.

Anal. Calcd. for $C_{26}H_{22}N_2$: C, 82.72, H, 6.14. Found: C, 82.91, 82.95; H, 6.18, 6.07.[10]

The mother liquors were combined and concentrated to a volume of 160 ml. by distillation. Chilling the solution yielded orange crystals which were recrystallized from 125 ml. of ethyl acetate to yield 0.60 g., m.p. 193–195°; total yield 11.50 g. (84%).

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1-Diazo-3-phenoxy-2-butanone[1]

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The cyclization of β-aryloxypropionic acids and their derivatives to chromanones is well-known. The present note describes a brief study of the Arndt-Eistert reaction for preparation of β-aryloxypropionic acids as potential chromanone precursors.

Phenoxyacetyl chloride (I) reacted with ethereal diazomethane (II) to give a yellow oil, presumably III. Utilization of silver oxide and water to effect Wolff rearrangement of III gave no appreciable yield of β-phenoxypropionic acid. The Newman-Beal modification[2] of the Wolff rearrangement, however, gave the crude methyl ester, which upon hydrolysis yielded β-phenoxypropionic acid,[3] although in low over-all yield.

$$\underset{\text{I, R = H}\quad \text{IV, R = CH}_3}{C_6H_5OCH(R)COCl} + \underset{\text{II}}{CH_2N_2} \longrightarrow C_6H_5OCH(R)COCHN_2 + \text{By-products}$$

III, R = H
V, R = CH_3

α-Phenoxypropionyl chloride (IV) gave with II the crystalline 1-diazo-3-phenoxy-2-butanone (V), which was purified by crystallization from benzene–petroleum ether. As is commonly done,[4] however, the crude diazoketone was employed in the Arndt-Eistert reaction. At least 33% of the V employed was recovered by vacuum distillation of the crude reaction product. The ester of the rearranged acid may have been present, but the data available indicated that the yield of such a product was low. It is apparent that V is unusually stable, both toward heat and metal ion catalysis as used in the Wolff rearrangement.[5]

EXPERIMENTAL[6]

Arndt-Eistert reaction with phenoxyacetyl chloride. An ether solution of diazomethane was prepared by the method of Arndt.[7] The intermediate nitrosomethylurea was prepared from 26 g. of *N*-acetyl-*N'*-methylurea according to the method of Amstutz and Myers.[8] A solution of 5.8 g. (0.034 mole) of phenoxyacetyl chloride in 20 ml. of dry ether was added dropwise over a period of *ca.* 30 min. to the dry diazomethane solution, cooled in ice, and protected by a calcium chloride drying tube. The reaction mixture was allowed to stand overnight at room temperature, and then the solvent was removed under reduced pressure at 20–30°. There remained a residual orange colored oil, which was dissolved in 55 ml. of absolute methanol and placed in a three-necked flask equipped with a mechanical stirrer and dropping funnel. The reaction flask was connected by a rubber hose to a 1-liter graduated cylinder inverted over a pan of water, thus providing a crude gasometer. A solution of 1.25 g. of silver benzoate in 11.4 g. of triethylamine was added over a period of 7 hr., with concomitant evolution of about 83% of the theoretical amount of nitrogen. The reaction mixture was heated under reflux for a few minutes, and the solvent then was removed under reduced pressure. An ether solution of the residual oil was washed first with 100 ml. of saturated sodium bicarbonate solution, then with 75 ml. of a 3% solution of hydrochloric acid. After drying over anhydrous magnesium sulfate, the solvent was removed and the residual oil distilled under reduced pressure. Two fractions were collected: (*a*) 1.00 g., b.p. 84–134° (24 mm.), n_D^{24}, 1.5183; and (*b*) 2.48 g., b.p. 134–138° (24 mm.), n_D^{24}, 1.5086. The literature[9] gives for methyl β-phenoxypropionate n_D^{20}, 1.5071 and b.p. 85° at 0.4 mm.

From a similar run, methyl β-phenoxypropionate (Fraction *b*, 1 g.) was hydrolyzed in 11 ml. of 0.5*N* sodium hydroxide, by heating on a steam bath for *ca.* 1 hr. The mixture was cooled, neutralized with concd. hydrochloric acid, and extracted with ether. The ether phase was then extracted with 5% sodium bicarbonate, which upon acidification gave white crystals of β-phenoxypropionic acid (0.12 g.),[10] m.p. 96–97° (lit.[11] m.p. 97–98°).

1-Diazo-3-phenoxy-2-butanone was prepared by the general method outlined in the preceding section. A solution of 12.4 g. (0.067 mole) of α-phenoxypropionyl chloride in 50 ml. of dry ether was added dropwise over a period of *ca.* 30 min. to a diazomethane solution prepared from the nitrosomethylurea from 49 g. of *N*-acetyl-*N'*-methylurea. The residual yellow oil from solvent removal solidified upon strong cooling. From a similar run, an analytical sample of the yellow

(1) Abstracted from a portion of a thesis submitted in partial fulfillment of requirements for the Ph.D. degree at the University of Nebraska by Loren L. Braun, 1956.

(2) M. S. Newman and P. F. Beal, *J. Am. Chem. Soc.*, **72**, 5161 (1950).

(3) Cyclization of β-phenoxypropionic acid to chromanone has been described by J. D. Loudon and R. D. Razdan, *J. Chem. Soc.*, 4299 (1954).

(4) W. E. Bachman and W. S. Struve, *Org. Reactions*, **I**, 48, 1942.

(5) A limited correlation is possible between our observation of unusual stability of V and that of H. R. Hensel [*Chem. Ber.*, **88**, 527 (1955)], who has noted that α-diazo-γ-(2,4-dichlorophenoxy)acetone retains nitrogen, even on heating with cupric oxide at 60° in petroleum ether, and at 100° with lead tetraacetate in dioxane.

(6) Melting points are uncorrected, and were observed in capillary tubes except where otherwise noted.

(7) F. Arndt, *Org. Syntheses*, **15**, 3 (1935).

(8) E. D. Amstutz and R. R. Myers, *Org. Syntheses*, Coll. Vol. II, 462 (1943).

(9) C. E. Rehberg and M. B. Dixon, *J. Am. Chem. Soc.*, **72**, 2205 (1950).

(10) The low yield of the acid is attributed either to impurity of the methyl ester (from incomplete Wolff rearrangement), or difficulty in controlling the hydrolysis of the pure ester. No decision appears possible between these alternative explanations at present.

(11) R. H. Hall and E. S. Stern, *J. Chem. Soc.*, 2035 (1949).

1-diazo-3-phenoxy-2-butanone was obtained by recrystallization from benzene–petroleum ether (b.p. 30–60°); m.p. 34–35° (Kofler hot stage[12]).

Anal. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.14; H, 5.30; N, 14.73. Found: C, 63.25; H, 5.47, N, 14.26.

Wolff rearrangement was attempted with the crude solid diazoketone (total residual product from the reaction described immediately above), by the general procedure previously outlined. Gas evolution ceased after 2.5 g. of silver benzoate in 22.5 g. of triethylamine had been added. Isolation of product in the usual manner gave a residual oil, which was distilled under reduced pressure. Three fractions were collected, one of which (4.21 g.), b.p. 110–120° (0.55–0.75 mm.), solidified upon strong cooling. Recrystallization from petroleum ether (b.p. 30–60°) gave a yellow crystalline product, m.p. 34–35°, which in alcohol solution yielded a gas (presumably nitrogen) upon acidification with hydrochloric acid, and was considered to be recovered 1-diazo-3-phenoxy-2-butanone.

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(12) L. Kofler, *Angew. Chem.*, **51**, 703 (1938).

3,3-Dimethyl-1,4-pentadiene[1]

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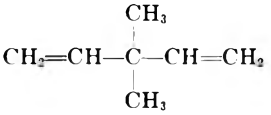
The previously unreported 3,3-dimethyl-1,4-pentadiene (I) is the simplest diene which cannot



conjugate by mere migration of a double bond. As such, we wished to study its catalytic hydrogenation. It is also of interest as model compound for other mechanistic studies.

The readily accessible[2] 1,5-dichloro-3,3-dimethylpentane (II) would seem an attractive starting material. However, attempts to dehydrochlorinate II directly with a variety of bases failed. The di-iodide corresponding to II reacts very rapidly to give good yields of I when refluxed with the hindered amine, 2-methylquinoline. This appears to be an example of the general rule that, in proceeding from chlorides to bromides to iodides, ease of dehydrohalogenation increases even more rapidly than that of nucleophilic substitution.

The preparation may be simplified by refluxing a mixture of II, sodium iodide and 2-methylquinoline under conditions such that the olefin is removed as it is formed.[3] This reaction is much slower than that of the di-iodide. The rate limiting step is apparently substitution of chloride by iodide. Presumably, the sequence of intermediates is chloro-iodide, chloroolefin, iodoolefin. Equally good results were obtained in converting 1-chloro-3,3-dimethylpentane to 3,3-dimethyl-1-pentene but the conversion[4] of 1-chloro-3,3-dimethylbutane to *t*-butylethylene failed, perhaps because of lower refluxing temperatures.

Pyrolysis over calcium chloride of II at about 550° or of the corresponding dibromide at about 450° gave small yields, 5–10%, of I plus a number of difficultly removable by-products.

EXPERIMENTAL

1,5-Dichloro-3,3-dimethylpentane was prepared following Schmerling and West.[2] We found it important to cool the 1,3-dichloro-3-methylbutane to −40° before adding aluminum chloride and to start the ethylene flow immediately. The reaction flask can then be warmed to −25° but ethylene must be fed as fast as it is absorbed. Under these conditions, little or no hydrogen chloride appears in the small amount of exit gas and the amounts of lower and higher molecular weight materials are minimal. Yields of 70% or better result from final distillation at reduced pressure; n_D^{20} 1.4643, reported[2] 1.4652.

3,3-Dimethyl-1,4-pentadiene (I). A mixture of 0.5 mole of II, 2 moles of 2-methylquinoline, and 0.1 mole of sodium iodide was refluxed in a flask surmounted by a tubing 40 cm. long with a standard taper plug at the top. Just before this was a connection to a small Vigreux column at the top of which was a condenser and take-off. The reflux had to be interrupted once during a run, the plug removed, and 2-methylquinoline hydrohalide which had distilled into the tubing scraped down into the flask. The reflux rate was maintained so that the temperature at the top of the Vigreux column was between 60 and 70°. The reaction is slow; a few hours elapse before diolefin appears and the entire reaction requires about 8 hr. The product was dried with sodium sulfate and fractionated; yield, 58% at b.p. 70.2° at 750.5 mm. Further possible purification was effected by storage over sodium and azeotropic distillation with methanol, n_D^{20} 1.4067; d_4^{20} 0.7017.

Anal. Calcd. for C_7H_{12}: C, 87.4; H, 12.6. Found: C, 87.9; H, 12.5.

The diolefin absorbs 2 moles of hydrogen in the presence of platinum oxide and forms a hydrocarbon with the infrared spectrum of 3,3-dimethylpentane.

3,3-Dimethyl-1-pentene was made in 88% yield from 1-chloro-3,3-dimethylpentane[5] by the same process, b.p. 77.2° at 755 mm.; n_D^{20} 1.3978.

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(4) W. O. Haag and H. Pines, private communication.
(5) L. Schmerling, *J. Am. Chem. Soc.*, **67**, 1152 (1945).

Lithium Cleavages of Triphenyl Derivatives of Some Group Vb Elements in Tetrahydrofuran

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Cleavage of various compounds with alkali metals has often proved to be a valuable tool in

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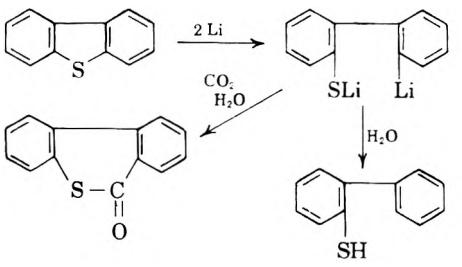
(2) L. Schmerling and J. P. West, *J. Am. Chem. Soc.*, **74**, 2885 (1952).

(3) We are indebted to Professor L. C. King for suggesting this one-step modification.

synthesis and structure proof. For the cleavage of some heterocycles, lithium in tetrahydrofuran[1] (THF) was found to be most effective.

While dibenzothiophene was not cleaved by lithium in diethyl ether even after 36 hr. at reflux, the use of refluxing dioxane[2] or tetrahydrofuran (THF) at room temperature[1] as solvents gave in addition to biphenyl, 2-mercaptobiphenyl of 3,4-benzothiocoumarin after hydrolysis or carbonation,



respectively. Dibenzo-*p*-dioxin, thianthrene, dibenzofuran, and diphenyl ether were also successfully cleaved by lithium in THF.[1]

On refluxing triphenylamine with lithium in the same solvent for 3 hr.[3] diphenylamine had been obtained in 9.7% yield, together with large amounts of unreacted starting material. In an extension of this work we noticed that after an induction period the cleavage of triphenylamine in this solvent proceeds smoothly even at room temperature. The reaction was started by employing first only a small amount of the solvent, the main part of which was added after Color Test I[4] had become positive. Carbonation after 4 hr. of stirring gave diphenylamine and benzoic acid in 59% and 25% yields, respectively.

$$(C_6H_5)_3N \xrightarrow{2\ Li} (C_6H_5)_2NLi + C_6H_5Li \xrightarrow{CO_2,\ H^+} (C_6H_5)_2NH + C_6H_5COOH$$

Other triphenyl derivatives of group Vb elements, such as triphenylphosphine, triphenylarsine, and triphenylstibine, were also easily cleaved by lithium in THF. In all cases the reactions were exothermic giving rise to a dark red or brown color; in the case of triphenylamine however, the resulting solution was deep green. Color Test I[4] usually was positive within one minute after the reaction was started.

The cleavage of triphenylphosphine to diphenylphosphinolithium[5] (I) and phenyllithium gave, after hydrolysis, diphenylphosphine in good yields, together with small amounts of its oxidation product, diphenylphosphinic acid. When the cleavage products were allowed to react with chlorotriphenylsilane, tetraphenylsilane was isolated in a 64% yield. The expected triphenylsilyldiphenylphosphine (II), however, has not been isolated. Only its hydrolysis and oxidation products, triphenylsilanol, diphenylphosphine, and diphenylphosphinic acid, were identified.

$$(C_6H_5)_3P \xrightarrow{2Li} (C_6H_5)_2PLi + C_6H_5Li \xrightarrow{H_2O}$$
$$(C_6H_5)_2PH \xrightarrow{[O]} (C_6H_5)_2P(O)OH$$
$$(C_6H_5)_3SiCl \downarrow \quad I$$
$$(C_6H_5)_4Si + [(C_6H_5)_2PSi(C_6H_5)_3] \xrightarrow{H_2O,\ [O]}$$
$$II$$
$$(C_6H_5)SiOH + (C_6H_5)_2PH + (C_6H_5)_2P(O)OH$$

The lithium cleavage products of triphenylarsine were reacted with chlorotrimethylsilane to give trimethylphenylsilane (76%), bis(diphenylarsenic) oxide (54%), and diphenylarsinic acid (3%) after hydrolysis and contact with air. Triphenylstibine similarly gave trimethylphenylsilane (62.5%) and diphenylstibinic acid (69.5%).

$$(C_6H_5)_3As \xrightarrow{2\ Li} C_6H_5Li + (C_6H_5)_2AsLi \xrightarrow{(CH_3)_3SiCl}$$
$$\xrightarrow{H_2O,\ [O]} (CH_3)_3SiC_6H_5 + [(C_6H_5)_2As]_2O + (C_6H_5)_2As(O)OH$$

$$(C_6H_5)_3Sb \xrightarrow{2Li} C_6H_5Li + (C_6H_5)_2SbLi \xrightarrow{(CH_3)_3SiCl}$$
$$\xrightarrow{H_2O,\ [O]} (CH_3)_3SiC_6H_5 + (C_6H_5)_2Sb(O)OH$$

The reaction of triphenylbismuthine and lithium in THF was not investigated, but a similar cleavage[5a] would be expected in this case also.

EXPERIMENTAL[6]

Cleavage of triphenylamine. Ten grams (0.0408 mole) of triphenylamine was cleaved in 80 ml. of THF with 2.1 g. (0.3 g.-atom) of finely cut lithium wire. The reaction was started by adding only a small amount of the solvent. After stirring for 0.5 hr. at room temperature the solution slowly turned brown, and a few minutes later deep green. Then the rest of the solvent was added slowly and the solution stirred for 4 additional hours. The reaction mixture was filtered through glass wool and carbonated in the usual manner. The resulting products were treated with dilute acid in order to destroy any possibly formed diphenylcarbamic acid, followed by the addition of some ether and extraction with dilute sodium hydroxide. The aqueous solution was acidified and extracted with ether. The removal of the solvent left a brown oil, which was subsequently extracted with boiling petroleum ether (b.p. 60–70°), using five 25-ml. portions. Recrystal-

(1) H. Gilman and J. J. Dietrich, *J. Org. Chem.*, **22**, 851 (1957).

(2) H. Gilman and D. L. Esmay, *J. Am. Chem. Soc.*, **75**, 2947 (1953).

(3) H. Gilman and J. J. Dietrich, *J. Am. Chem. Soc.*, **80**, 380 (1958).

(4) H. Gilman and F. Schulze, *J. Am. Chem. Soc.*, **47**, 2002 (1925); G. Wittig, *Angew. Chem.*, **53**, 243 (1940).

(5) The preparation and properties of the corresponding sodium compound have recently been described by W. Kuchen and H. Buchwald, *Angew. Chem.*, **69**, 307 (1957).

(5)(a) Prof. W. Rüdorff kindly informed us recently that triphenylphosphine, -arsine, and -stibine have also been successfully cleaved by sodium in liquid ammonia. See Walter Müller, Dissertation, Tübingen (1957).

(6) All melting points and boiling points are uncorrected. The tetrahydrofuran was dried and purified by successively shaking with sodium hydroxide pellets, refluxing over sodium metal for at least 24 hr., and finally distilling immediately before use from lithium aluminum hydride. The cleavage reactions were carried out in an atmosphere of dry, oxygen-free nitrogen.

lization of the resulting product from water gave 1.2 g. (24.5%) of benzoic acid, m.p. 120–121.5°, identified by mixture melting point.

The neutral organic layer was distilled and the residue chromatographed on alumina. The product eluted with petroleum ether (b.p. 60–70°) and carbon tetrachloride was recrystallized from petroleum ether of the same boiling point to give 4.05 g. (59%) of diphenylamine, m.p. 53–54°, identified by mixture melting point and infrared spectra.

When a mixture of 12.25 g. (0.05 mole) of triphenylamine, 1 g. (0.15 g.-atom) of lithium, and 50 ml. of THF was stirred for 1.5 hr. at room temperature and refluxed for 3 additional hours,[6a] a brown color had developed, but Color Test I[4] was still negative. After hydrolysis, 8.3% of diphenylamine was isolated, together with 58% of triphenylamine. In another experiment,[6a] employing the same amount of starting materials and solvent, a positive Color Test I was obtained after 3 hr. at reflux. Subsequent carbonation gave no benzoic acid, but diphenylamine in a 9.7% yield, together with unreacted triphenylamine (60%).

Cleavage of triphenylphosphine. To a stirred mixture of 10 g. (0.0382 mole) of triphenylphosphine and 1.4 g. (0.2 g.-atom) of finely cut lithium wire was added slowly 100 ml. of THF. The reaction started immediately, the solution turned dark red, heat was evolved, and Color Test I[4] was positive. Stirring was continued for 1 hr., at which time the mixture had cooled to room temperature. The solution was filtered through glass wool, hydrolyzed, and after the addition of some ether, extracted with dilute acid and water. The dried organic layer was distilled to give 5.2 g. (68.5%) of diphenylphosphine, b.p. 150–154° (11 mm.).[7] The infrared spectrum showed the characteristic P-H absorption band at 4.4μ.

In a second experiment 15.0 g. (0.0572 mole) of triphenylphosphine was cleaved with 1.4 g. (0.2 g.-atom) of lithium in 100 ml. of THF at −10° to 0° (stirring for 4 hr.). The work-up in the manner described above gave 4.95 g. (47%) of diphenylphosphine, b.p. 150–154° (11 mm.). The distillation residue was recrystallized from ethanol and yielded 2.5 g. (20.2%) of diphenylphosphinic acid, m.p. 190–191.5°, which was identified by its infrared spectrum.

In a third experiment the cleavage products were allowed to react with chlorotriphenylsilane. After hydrolysis, tetraphenylsilane, m.p. 232–234°, was isolated in a 64% yield from the ether insoluble part of the reaction mixture. Chromatography of the ether soluble part gave crude triphenylsilanol, diphenylphosphinic acid, and diphenylphosphine, which were identified by their infrared spectra.

Cleavage of triphenylarsine. To a stirred mixture of 10 g. (0.034 mole) of triphenylarsine and 1.4 g. (0.2 g.-atom) of finely cut lithium wire was added slowly 100 ml. of THF. The reaction started immediately, the solution turned red and showed a positive Color Test I.[4] After stirring for 1 hr. while cooling with ice and one additional hour at room temperature, a solution of 7.4 g. (0.068 mole) of chlorotrimethylsilane in 10 ml. of THF was added. The color of the solution faded after the addition of the second equivalent. The work-up by filtration through glass wool, addition of some ether, extraction with dilute acid, drying of the organic layer with sodium sulfate, and distillation gave 3.9 g. (76%) of trimethylphenylsilane, b.p. 166–169°, n_D^{20} 1.4870, which was identified by its infrared spectrum. The high boiling fractions, 1.5 g., b.p. 160–230° (0.1 mm.), and 5.1 g., b.p. 230–240° (0.1 mm.), both yellow oils, which slowly solidified, were treated with cold benzene. The benzene insoluble part was recrystallized from water to give 0.25 g. (3%) of diphenylarsinic acid, m.p. 171–172.[8] The benzene soluble part was recrystallized from ethanol to give 4.3 g. (54%) of bis(diphenylarsenic) oxide, m.p. 92–93.5°.[8]

Cleavage of triphenylstibine. The cleavage of 10 g. (0.0283 mole) of triphenylstibine with 1.4 g. (0.2 g.-atom) of lithium in 80 ml. of THF was carried out as described in the previous experiment. The cleavage products were allowed to react with 6.5 g. (0.06 mole) of chlorotrimethylsilane. The deep red-brown color faded immediately, leaving a small amount of black precipitate (apparently metallic antimony). The reaction mixture was filtered through glass wool, hydrolyzed, and after the addition of some ether, washed with dilute acid. The dried organic layer deposited on standing a white precipitate, which was filtered off, washed with ether and water to give 5.25 g. (60%) of diphenylstibinic acid, m.p. 283–286°.[9] Distillation of the filtrate yielded 2.65 g. (62.5%) of trimethylphenylsilane, b.p. 55–60° (10 mm.), n_D^{20} 1.4865, which was identified by its infrared spectrum. The distillation residue upon treatment with benzene left 0.85 g. (9.5%) of insoluble diphenylstibinic acid, m.p. 282–286°. Addition of petroleum ether (b.p. 60–70°) to the benzene solution gave 0.2 g. (2%) of a colorless, crystalline compound, m.p. 170–172°, which is thought to be diphenylantimony trichloride.[9]

Relevant to the studies now reported are some experiments in progress on the reaction of triphenylsilyllithium with inorganic salts as well as with aryl derivatives like those described in this paper.

Acknowledgment. This research was supported by the United States Air Force under Contract AF 33(616)-3510 monitored by Materials Laboratory, Directorate of Laboratories, Wright Air Development Center, Wright-Patterson AFB, Ohio. Infrared analyses were obtained through the courtesy of the Institute for Atomic Research, Iowa State College, and special acknowledgment is made to Miss M. Powers for the spectra.

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(6) (a) Experiments of J. J. Dietrich.

(7) S. I. Vol'fkovich, V. K. Kustov, and K. F. Koroteeva, *Izvest. Akad. Nauk, S.S.S.R., Otdel. Khim. Nauk*, 1954, 5 [*Chem. Abstr.*, 49, 6859 (1955)] report a boiling point of 272° (760 mm.) and 170° (3 mm.) for diphenylphosphine.

(8) W. La Coste and A. Michaelis, *Ann.*, 201, 229, 231 (1880), report a melting point of 174° for diphenylarsinic acid and a melting point of 91–92° for bis(diphenylarsenic) oxide.

(9) H. Schmidt, *Ann.*, 421, 236 (1920) reports a melting point of 285° for diphenylstibinic acid and a melting point of 175° for diphenylantimony trichloride.

Reaction of Xanthates with β-Propiolactone

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Received January 10, 1958

The reaction of β-propiolactone with a variety of nucleophilic reagents has been described during the last decade. An excellent review on this subject has appeared recently.[1] As described in this article, β-propiolactone can react either at the carbonyl carbon to produce derivatives of β-hydroxypropionic acid or at the β-carbon to produce β-carboxyethyl derivatives of the nucleophile. The course of

(1) H. E. Zaugg, *Org. Reactions*, VIII, 305 (1954).

TABLE I

3-MERCAPTOPROPIONIC ACID, ALKYL XANTHATES

Potassium Alkyl Xanthate	Yield, %	Melting Point	Refractive Index (n_D^{25})	Calcd. for	Analysis C	H	S	Found: C	H	S
Methyl	100	—	1.5511	$C_5H_8O_3S_2$	33.3	4.47	35.6	33.5	4.57	35.9
Ethyl	95	70–71°	—	$C_6H_{10}O_3S_2$	37.1	5.19	33.0	37.3	5.08	33.3
n-Propyl	99	50–53°	—	$C_7H_{12}O_3S_2$	40.3	5.81	30.8	40.2	5.81	30.8
Allyl	97	—	1.5505	$C_7H_{10}O_3S_2$	40.7	4.89	31.1	40.4	5.01	31.3
n-Butyl	100	—	1.5333	$C_8H_{14}O_3S_2$	43.2	6.35	28.8	43.3	6.46	29.2
2-Ethylhexyl	100	—	1.5177	$C_{12}H_{22}O_3S_2$	51.8	7.97	23.0	51.3	7.86	23.0

the reaction depends on a number of factors including the nature of the attacking reagent, solvent employed, and reaction conditions.

Although mercaptans and other organic sulfur compounds have been studied as nucleophiles, the reaction of xanthates with β-propiolactone has not been reported. In the present study it has been found that essentially quantitative yields of β-carboxyethyl xanthate esters are produced when β-propiolactone and potassium xanthates are allowed to react in aqueous solution at 20–30°.

$$ROCSSK + CH_2CH_2CO \longrightarrow$$

$$ROCSSCH_2CH_2{-}COOK \xrightarrow{H^+} ROCSSCH_2CH_2COOH$$

Table I summarizes the results of this investigation.

Certain of these products possess interesting fungicidal, herbicidal, and microbiological activity.

EXPERIMENTAL

The potassium alkyl xanthates employed were freshly prepared from alcoholic potassium hydroxide and carbon disulfide. Freshly distilled β-propiolactone was used in these experiments. The reaction of potassium ethyl xanthate with β-propiolactone is typical of the general procedure employed and will be discussed in detail.

To a solution of 8.0 g. (0.05 mole) of potassium ethyl xanthate in 100 ml. of water at 15–20° was added 3.7 g. (0.05 mole) of β-propiolactone over a 10-min. period. Occasional cooling was necessary to maintain the temperature below 20°. After an additional 2-hr. period at room temperature, the solution was acidified with hydrochloric acid whereupon a white crystalline solid separated. This solid was removed by filtration and was washed with water. After drying in a vacuum desiccator, there was obtained 9.4 g. of product, m.p. 69–70°. Recrystallization from Skellysolve B yielded 9.2 g. (95%) of 3-mercaptopropionic acid, ethyl xanthate, m.p. 70–71°.

In a similar manner the potassium alkyl xanthates listed in Table I were reacted with β-propiolactone. In the case of liquid products, isolation was accomplished by solvent extraction after acidification, water washing, drying, and evaporation of the solvent. Analytical data in Table I are on the products as isolated in this manner. Purification by vacuum distillation was not entirely satisfactory as there was evidence of decomposition at temperatures above 140–150°.

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Reaction of Cyclohexanone and Hydrogen Peroxide with Ferrous Sulfate and Dimethyl Maleate

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The reaction of cyclohexanone peroxide (I) (formed *in situ* from cyclohexanone and hydrogen peroxide) with ferrous ion in the presence of butadiene to give dimethyl 8,12-eicosadiene-1,20-dioate was recently reported.[1]

We have now found that dimethyl maleate will also react with the intermediate radical A[2] to give a corresponding dimeric product, II. The latter was isolated, after esterification, as a reasonably pure distillation residue (38% yield based on unrecovered ketone, 39% based on unrecovered dimethyl maleate, 35% on hydrogen peroxide) after removal of the more volatile 1:1 products, III and IV (33% yield based on unrecovered ketone).[3] Analysis of the mixture of III and IV by carbon and hydrogen values, iodine number and by quantitative hydrogenation indicated it to contain 91% of III and 9% of IV.

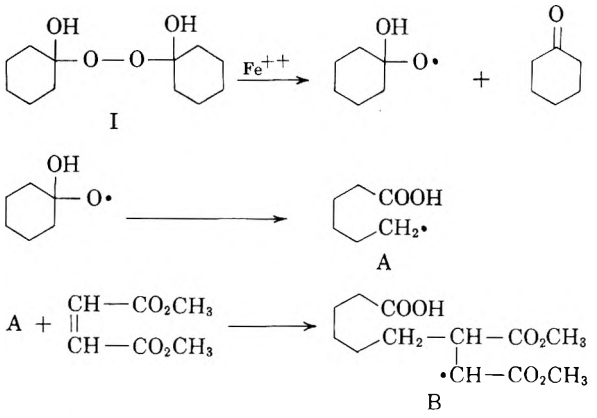
Saponification of this hydrogenated ester mixture afforded the water-soluble 3-carboxyazelaic acid (V), an apparently novel compound.

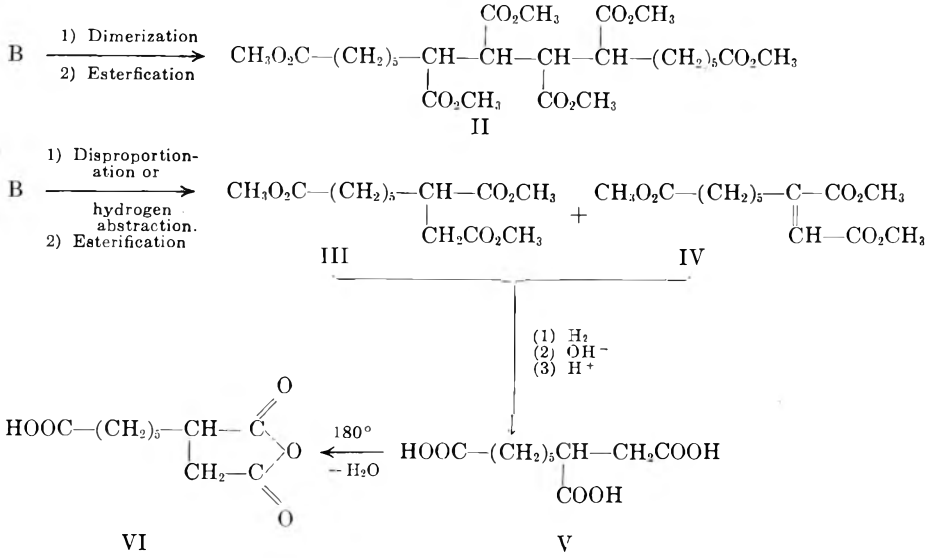
When V was heated at 180° and 1 mm. for six hours, one molecule of water was lost and a water-insoluble anhydride was formed. The infrared spectrum of the latter was compatible with that expected for the substituted succinic anhydride, VI.

(1) M. S. Kharasch and W. Nudenberg, *J. Org. Chem.*, 19, 1921 (1954).

(2) *Cf.* ref. 1, footnote 4, for a brief discussion of the possible existence of A.

(3) No comparable lower molecular weight products were observed in the reaction of I with iron and butadiene (ref. 1).





EXPERIMENTAL

Reaction of cyclohexanone and hydrogen peroxide with ferrous sulfate and dimethyl maleate. To a solution of 50 g. of concentrated sulfuric acid in 750 ml. of methanol was added 196 g. (2.0 moles) of cyclohexanone, keeping the temperature below 30° by external cooling. To this solution was then added portionwise 1 mole of 30% hydrogen peroxide, again keeping the temperature below 30° by cooling.

The cyclohexanone peroxide solution thus prepared was added dropwise with stirring at 20–25° over a 2 hr. period to a mixture of 292 g. (1.05 mole) of ferrous sulfate heptahydrate, 850 ml. of water, 150 g. of concentrated sulfuric acid, 300 ml. of methanol, and 180 g. (1.25 moles) of dimethyl maleate (n_D^{20} 1.4418) contained in a 3-liter, 3-neck round-bottom flask.

After completion of the addition, stirring was continued for 15 min. before the mixture was poured into 2 l. of water and extracted with three 500 ml. portions of chloroform. The combined chloroform extract was washed with water, dried over magnesium sulfate, and concentrated on the steam bath. The concentrate, on distillation through a 1 × 50 cm. glass helices packed column, gave the following fractions after removal of the last traces of solvent.

Fraction 1: 82–84° (80 mm.), 108 g.; Fraction 2: 84–65° (80–20 mm.), 11 g.; Fraction 3: 65–98° (20 mm.), 3 g.; Fraction 4: 98–65° (20–1 mm.), 66 g., n_D^{20} 1.4420. Residue, 196 g. Fractions 1 and 2 were combined; titration with hydroxylamine hydrochloride indicated the presence of 104 g. (1.06 mole) of recovered cyclohexanone. Fraction 4 was recovered dimethyl maleate (0.46 mole) identified by boiling range and refractive index.

The residue was esterified by refluxing overnight in 1000 ml. of methanol containing 5 g. *p*-toluenesulfonic acid catalyst. A slight excess of potassium hydroxide in water was then added to neutralize the catalyst and the mixture was concentrated to low volume on the steam bath. The concentrate was taken up in 1000 ml. of chloroform and washed with 200 ml. of 5% potassium carbonate solution and then with water. After removal of chloroform on the steam bath, the crude ester mixture was distilled through the packed column to a maximum kettle temperature of 270°. The following fractions were obtained:

Fraction 5: 50–152° (1 mm.), 10 g.; Fraction 6: 152–158° (1 mm.), 85 g., n_D^{20} 1.4464. Residue, 98 g.

Analysis of Fraction 6 was in agreement for a mixture containing 91% by weight of dimethyl-3-carbomethoxyazelate and 9% of dimethyl-3-carbomethoxy-2-nonene-1,9-dioate (33% based on unrecovered cyclohexanone).

Anal. Calcd. for 91% $C_{13}H_{22}O_6$ and 9% $C_{13}H_{20}O_6$: C, 56.9; H, 8.1; sapon. equiv., 92; iodine no., 9. Found: C, 56.9; H, 8.1; sapon. equiv., 93; iodine no., 9.

Analysis of the residue was in fair agreement for dimethyl 7,8,9,10-tetracarbomethoxy-1,16-hexadecanedioate (38% yield based on unrecovered ketone).

Anal. Calcd. for $C_{26}H_{42}O_{12}$: C, 57.1; H, 7.7; sapon. equiv. 91. Found: C, 57.3; H, 7.5; sapon. equiv. 98.

3-Carboxyazelaic acid. Sixty grams (0.219 mole) of Fraction 6 above was dissolved in 150 ml. of ethanol and shaken with hydrogen at room temperature and 50 pounds pressure using 10 g. of 5% palladium-on-charcoal catalyst. After 30 min., 0.018 mole of hydrogen had been absorbed and the uptake was negligible during an additional 5 hr. After removal of the catalyst by filtration, there was added a solution of 33 g. of sodium hydroxide in 150 ml. of water; the mixture was allowed to reflux overnight on the steam bath. The water-soluble product was isolated by acidification with 75 ml. of concentrated hydrochloric acid, followed by concentration to an oily residue containing sodium chloride. After trituration with warm acetone, salt was removed by filtration, and the acetone solution was adjusted to a volume of 125 ml. An equal volume of benzene was added, followed by enough petroleum ether to effect a phase separation. Long chilling produced 35 g. of a hard crystalline mass on the surface, m.p. 64–72°. Recrystallization from acetone-chloroform (1:3) afforded 27 g. of β-carboxyazelaic acid, m.p. 64–67°, containing one quarter of a molecule of chloroform of crystallization.

Anal. Calcd. for $C_{10}H_{16}O_5 \cdot {}^1/_4CHCl_3$: C, 47.0; H, 6.3; Cl,

10.1; neut. equiv., 88. Found: C, 47.5; H, 6.4; Cl, 9.0; neut. equiv., 88.

After drying for 15 hr. at 60° and 5 mm., the neut. equiv. had fallen to 80.7; further drying at 80° and 2 mm. for 24 hr. caused the N.E. to drop to 78.1 and the material was reanalyzed.

Anal. Calcd. for $C_{10}H_{16}O_6$: C, 51.7; H, 6.9; neut. equiv., 77.4. Found: C, 51.9; H, 6.9; neut. equiv. 78.1. The melting point of the solvent-free acid was 83–84°.

A two gram sample of acid (m.p. 64–67°) lost the theoretical amount of chloroform when heated for 2 hr. at 120° and 1 mm. The same sample, when heated further at 180° and 1 mm. pressure for 6 hr. lost an additional weight corresponding to the loss of 1 molecule of water. The crude *anhydride* thus obtained melted at 81–83°; after crystallization from benzene-petroleum ether, it melted at 80–81°.

Anal. Calcd. for $C_{10}H_{14}O_5$: C, 56.1; H, 6.5; sapon. equiv., 72. Found: C, 56.3; H, 6.8; sapon. equiv., 73.

The infrared spectrum (KBr pressed plate) exhibited absorptions at 5.35 and 5.61μ; succinic anhydride absorption occurs at 5.36 and 5.61μ.[4]

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(4) H. M. Randall, R. G. Fowler, N. Fuson, and J. R. Dangl, *Infrared Determination of Organic Structures*, D. Van Nostrand Co., Inc., New York, 1949, p. 163.

p-Nitrophenylsemicarbazones of Trioses and Carbonyl Compounds of Biochemical Interest

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Received January 16, 1958

The derivatives of *p*-nitrophenylsemicarbazide with carbonyl compounds of biological origin are of interest in that they may offer a means of isolation and identification of the latter substances. It was of particular interest to us to secure a tool for the analysis of trioses. Earlier we have reported the preparation of *p*-phenylazophenylsemicarbazones of trioses and biologically related carbonyl compounds.[1] These derivatives were found unsatisfactory as analytical tools. In a search for a quantitative precipitant for glucose, Barré and Piché[2,3] prepared 4-substituted semicarbazides and obtained *p*-nitrophenylsemicarbazones of acetone, pyruvic acid, glyoxylic acid, and glucose among others. The presence of a nitrophenyl group in the *p*-nitrophenylsemicarbazones should provide an intense coloration by its derivatives in alkaline solution. This property of possible analytical application merited expoloration; consequently, *p*-nitrophenylsemicarbazones of the above mentioned trioses and several carbonyl compounds of biochemical interest were synthesized.

The one-step synthesis of *p*-nitrophenylsemicarbazide from the commercially available *p*-nitrophenyl isocyanate and the preparation of *p*-nitrophenylsemicarbazones are described in this report. Barré and Piché have obtained *p*-nitrophenylsemicarbazide by different methods.[2] However, the simple conversion of isocyanate into semicarbazide with anhydrous hydrazine was not attempted. This conversion has been carried out with good yield in this laboratory. The *p*-nitrophenylsemicarbazide thus obtained was converted into its hydrochloride to increase its solubility in water. Mixing of a saturated solution of the semicarbazide hydrochloride in 0.1*N* hydrochloric acid with an aqueous solution of the carbonyl compound yields the corresponding semicarbazone at room temperature. Crude semicarbazones are purified by recrystallization from ethanol or acetic acid.

All except one of the *p*-nitrophenylsemicarbazones prepared decompose at melting temperatures; therefore, these derivatives appear to be of little value for the identification of carbonyl compounds by melting point. Paper chromatography of the *p*-nitrophenylsemicarbazones was investigated for possible analytical application and the results will be reported elsewhere. The high extinction coefficients of the solutions of these derivatives in the ultraviolet range and the intense coloration on the addition of alkali to these solutions indicate that a promising reagent for the analysis of trioses and the carbonyl compounds of biochemical interest has been found.

EXPERIMENTAL

p-Nitrophenyl isocyanate, acetaldehyde, and ethyl acetoacetate were obtained from the Distillation Products Industries; acetaldehyde was redistilled just before use. Other starting material from various sources were used without further purification. Dihydroxyacetone was obtained from Dougherty Chemical Co. Glyceraldehyde, *alpha*-ketobutyric acid, *alpha*-ketoglutaric acid, and sodium *beta*-phenylpyruvate were from Sigma Chemical Co. Crude pyruvaldehyde (30% aqueous solution) was from Bios Laboratories, Inc. Oxalacetic acid and crude barium oxalosuccinate were from California Foundation for Biochemical Research.

Melting points are corrected. Absorption maxima, λ_{max}, and molar extinction coefficients, ϵ, were determined in ethanol unless otherwise indicated; a 0.001% solution was used for the determinations with a Beckman DU spectrophotometer.

p-Nitrophenylsemicarbazide. Commercial *p*-nitrophenyl isocyanate was partially purified by filtration in its molten state through a filter paper using a heated funnel. In 250 ml. of anhydrous toluene, 29 g. of the isocyanate was dissolved and the solution was directly filtered into a 1 l. 3-neck flask to remove the small amount of insoluble residue. A suspension of 9 ml. of anhydrous hydrazine in 350 ml. of anhydrous toluene was added dropwise into the isocyanate solution in 45 min. while vigorous stirring of the latter was maintained. Heat was generated by the reaction and immediate precipitation of an orange colored product was observed. The reaction flask was stoppered and allowed to stand overnight. The precipitate was collected on a funnel and washed with toluene, followed with petroleum ether (30–60°). The solvent was removed under vacuum in a desiccator. The crude product (33.7 g.) was recrystallized from boiling absolute ethanol yielding 22.0 g. (63%) of yel-

(1) M. U. Tsao and E. Van Dyke, *J. Am. Chem. Soc.*, **77**, 6693 (1955).

(2) R. Barré and L. Piché, *Can. J. Research*, **19B**, 158 (1941).

(3) R. Barré and L. Piché, *Can. J. Research*, **20B**, 17 (1942).

low needle-like crystals, m.p. 185–188° (reported 191° dec.[2]).

p-Nitrophenylsemicarbazide hydrochloride. This compound was prepared by dissolving 2 g. of *p*-nitrophenylsemicarbazide in 100 ml. of boiling absolute ethanol and adding 1 ml. of concentrated hydrochloric acid. Crystalline product in quantitative yield was obtained on cooling, m.p. 239° dec. (reported 265° dec.[2]).

p-Nitrophenylsemicarbazones. The general procedure for the preparation is described here. A saturated solution of *p*-nitrophenylsemicarbazide hydrochloride in 0.1*N* hydrochloric acid containing 1 or 2 millimole of the reagent was mixed with 1 millimole of the carbonyl compound dissolved in minimal amount of water or 0.1*N* hydrochloric acid. The precipitate thus obtained was collected on a glass funnel and washed with water. The crude product was dried and purified by recrystallization from ethanol, 50% ethanol, glacial acetic acid, or 50% acetic acid as indicated in Table I.

TABLE I

p-NITROPHENYLSEMICARBAZONES R=N—NH—C_6H_4—NO_2

	R	Yield, %	M.P.	Solvent for Recrystallization
1.	CH_3CH=	62	200° dec.	Ethanol
2.	$(CH_2OH)_2C$=	62	192° dec.	Ethanol
3.	CH_2OH—CHOH—CH=	52	196° dec.	Ethanol
4.	CH_3C(=)HC=	20	246° dec.	Acetic acid
5.	C_2H_5C(=)COOH	57	205° dec.	Acetic acid
6.	HOOC$(CH_2)_2C$(=)COOH	85	181° dec.	50% Ethanol
7.	(C_2H_5)OOCCH_2C(=)CH_3	69	174–175°	Ethanol
8.	HOOCCH_2C(=)COOH	65	219° dec.	50% Acetic acid
9.	HOOC(=)HOOCCH(=)$HOOCCH_2$	7	150° dec.	Acetic acid
10.	HOOC(=)$CH_2.C_6H_5$	66	197° dec.	Acetic acid

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Isolation of Two Sodium Methazonates

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Received January 20, 1958

Methazonic acid is usually prepared by the action of concentrated sodium hydroxide solution on nitromethane.[1]

Various attempts have been made to formulate a mechanism for the reaction but with little success. Levy and Rose[2] stated that an intermediate monosodium compound I is formed by the interaction of nitromethane and its sodium salt. This is then dehydrated to form monosodium methazonate II.

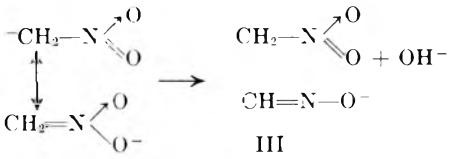
O_2N—CH_2—CH_2—N(OH)—ONa ⟶

I

HO—N=CH—CH=NO_2Na

II

Drew, McNesby, and Gordon,[3] however, who studied the reaction spectrophotometrically, stated that the methazonate anion III is formed by the reaction of two nitromethane anions, although the structure III would involve the formation of hydroxyl ions in a strongly alkaline medium.



III

The work reported in this paper shows that the reaction product is a disodium salt IV which is probably monohydrated. This then forms a hexahydrate which can be readily isolated from the solution.

TABLE II

p-NITROPHENYLSEMICARBAZONES R=N—NH—C_6H_4—NO_2

	Analysis							
	Carbon, %		Hydrogen, %		Nitrogen, %			
R	Calcd.	Found	Calcd.	Found	Calcd.	Found	λ_{max}	ϵ
1.	48.65	48.69	4.54	4.89	25.22	25.55	322	186,000
2.	44.77	44.64	4.51	4.25	20.89	20.76	322	213,000
3.	44.77	45.01	4.51	4.35	20.89	20.21	323	183,000
4.	47.66	47.30	3.77	3.81	26.16	26.86	331[a]	640,000[a]
5.	47.14	47.06	4.32	4.25	19.99	19.40	319	228,000
6.	40.00[b]	40.02	4.48[b]	4.40	15.55[b]	15.66	317	201,000
7.	50.65	50.83	5.23	5.65	18.18	17.94	322	197,000
8.	42.59	42.90	3.25	3.54	18.06	18.02	318	216,000
9.	42.40	42.96	3.29	3.42	15.22	15.09	319	208,000
10.	56.14	55.96	4.12	4.15	16.37	16.22	318	216,000

[a] In glacial acetic acid. [b] On basis of two moles of water of crystallization.

^-O—N=CH—CH=NO_2^-

IV

The formation of a disodium salt supports Drew's

(1) W. Meister, *Ber.*, **40**, 3535 (1907).

(2) N. Levy and J. D. Rose, *Quart. Revs.* (*London*), **1**, 358 (1947).

(3) C. M. Drew, J. R. McNesby, and A. S. Gordon, *J. Am. Chem. Soc.*, **77**, 2622 (1955).

proposed mechanism and is more acceptable on theoretical grounds than the formation of the monosodium salt III since it does not require the elimination of hydroxyl ion.

EXPERIMENTAL

Sodium methazonate was prepared using part of the procedure described by Meister[1] for the preparation of the acid. Nitromethane (8.5 ml.) was run in small portions into a cold stirred solution of 10 g. sodium hydroxide in 20 ml. water. The temperature of the solution was not allowed to exceed 40°. White crystals of the sodium derivative were formed; these dissolved slowly and the solution became first yellow and then deep cherry red. When the solid had completely dissolved, the solution was warmed for a few minutes at 50–55°.

At this stage, the methazonic acid is normally liberated by acidification but to obtain the intermediate sodium salt, the solution was cooled to 5–10° when it became viscous and solidified more or less completely. Absolute alcohol was added to aid filtration and the cream colored solid filtered off. This was decolorized further by solution in a minimum of water followed by precipitation with ice-cold alcohol. An almost white solid was obtained; this was dried with alcohol and ether.

RESULTS AND DISCUSSION

Titration of the sodium salt. Potentiometric titration of a solution of the sodium salt with 0.1N hydrochloric acid gave a titration curve (Fig. 1a) with a sharp change in *p*H around 9.5 and

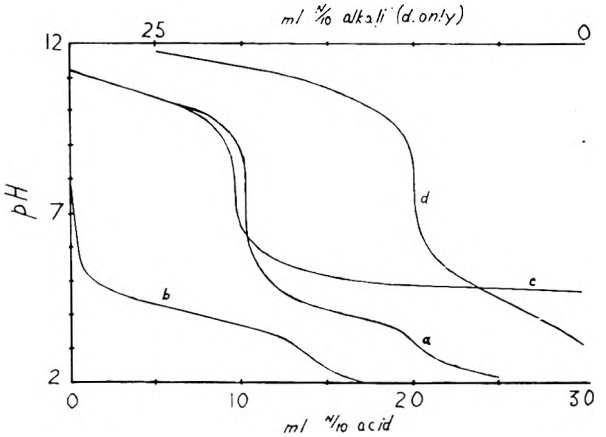


Fig. 1. Titration curves. *a.* Disodium methazonate. *b.* Monosodium methazonate. *c.* Disodium methazonate–acetic acid. *d.* Methazonic acid.

an inflection at *p*H × 3. The end point at *p*H 9.5 corresponded to an equivalent weight of about 260: monosodium methazonate has an equivalent weight of 126.

In view of this, similar titrations were carried out on a number of different preparations but an equivalent in the range 258–261 and a second point of inflection at *p*H 3 were always obtained. The titration curve is reversible when the liberated acid is back titrated without much delay.

Analysis of the sodium salt. Combustion analysis was impractical as the sodium salt deflagrated on heating. Determination of nitrogen by a modified Kjeldahl method and of sodium by flame photometry gave the following results.

N 10.7%; Na 18.8%

Loss in weight of the sodium salt. When the sodium salt was dried *in vacuo* over P_2O_5, a very hygroscopic pale yellow solid was obtained. The loss in weight was 35.9%.

These results correspond to a hydrated disodium salt. The hexahydrate corresponding to IV has the following composition.

Equiv. weight 256; N 10.8%; Na 18.0%

A loss in weight on drying of 35.9% corresponds to the loss of only 5 molecules of water of crystallization (theoretical 35.2%). The vacuum-dried material was analyzed. The results below are compared with those calculated for a monohydrate.

Calculated: equiv. wt. 166; N 16.9%; Na 27.7%
Found: equiv. wt. 172; N 16.2%; Na 28.0%

That the dried solid still contains water of crystallization was confirmed by infrared analysis. The final molecule of water is thus very tenaciously held, which suggests that a monohydrate is formed as the primary product of the reaction.

Isolation of monosodium methazonate. The cold cherry-red solution obtained in the above preparation was titrated with 10*N* hydrochloric acid to *p*H × 4.3, the temperature being maintained below 10°. A yellowish white solid crystallized out. This was filtered off, washed with a minimum of alcohol, and again precipitated from concentrated aqueous solution with ice-cold alcohol. It did not lose weight on keeping *in vacuo* over P_2O_5; its analysis gave the following results, which are compared with values calculated for monosodium methazonate II.

Calculated: equiv. wt. 126; N 22.2%; Na 18.2%
Found: equiv. wt. 129; N 21.2%; Na 18.1%

The titration curve (Fig. 1b) was almost identical with the second part of that of the disodium salt.

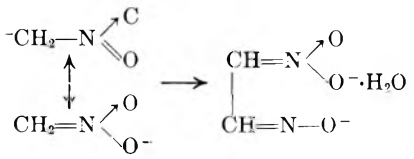
Methazonic acid. The point of inflection at *p*H 3 of the sodium methazonate titration corresponds to the titration of the nitroxylate ion $=N\begin{matrix}O\\ \diagup\\ \diagdown\\ O^-\end{matrix}$ so that the product of acidification is the aci-nitro form. This is unstable but a strong acid; as would be expected, the titration curve with acetic acid (Fig. 1c) does not show the second point of inflection. The instability of the aci-form would account for the formation of a red oil which always occurs in the preparation of the acid by this method.

The reversibility of the titration indicates that the aci-nitro group can be back-titrated with alkali if this is done without isolating the acid. When a prepared specimen of methazonic acid was

titrated potentiometrically with 0.1*N* sodium hydroxide however, the titration curve (Fig. 1d) showed only one sharp change in *p*H (corresponding to an equivalent of 104) and no other point of inflection.

Methazonic acid therefore normally functions as a monobasic acid $O_2NCH_2CH{=}NO^-H^+$ but in its preparation from nitro methane, an intermediate disodium salt is formed.

Bearing in mind that Drew's kinetic studies showed that the reaction involved two univalent negative ions, a more correct representation of its formation is therefore



although an intermediate compound could well be formed.

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Reaction of 1-Chloroisoquinoline with Peracetic Acid[1]

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As part of an investigation[2,3] of the rearrangement of isoquinoline-*N*-oxides, attempts were made to prepare 1-chloroisoquinoline-*N*-oxide by the reaction of 1-chloroisoquinoline with aqueous peracetic acid. Oxidations of this type have been effected with 2-bromopyridine using 40% peracetic acid[4] and with other α-halo-heterocycles. The desired oxide was not obtained, for the reaction took another course, but since several new isoquinoline derivatives were prepared, and since certain of the transformations were unexpected, the results are reported here.

When 1-chloroisoquinoline[5] was heated with acetic acid and hydrogen peroxide at 65°, a substance with the anticipated composition was obtained in consistently low yield, along with much colored, polymeric material. On treatment of the purified product with acetic anhydride, an acetyl derivative was formed, which, however, reverted to the starting material on hydrolysis. The oxidation product was eventually shown to be 4-chloroisocarbostyril by hydrogenolysis to isocarbostyril and by conversion to the known[5] 1,4-dichloroisoquinoline. Further, 1,4-dichloroisoquinoline, which may be prepared more conveniently by the action of phosphorus pentachloride on isocarbostyril[6] than by the method of Gabriel and Colman, was converted to 4-chloroisocarbostyril by methanolysis of the 1-chloro group and subsequent cleavage of the ether with hydrochloric acid.

It was found that the mode of formation of the unexpected product involved a surprisingly facile hydrolysis of the 1-chloroisoquinoline, followed by chlorination of the resulting isocarbostyril by the free halogen formed from the chloride ion liberated in the oxidizing medium. Although acid-catalyzed nucleophilic substitutions with 1-chloroisoquinoline are well known,[7] the conditions of the attempted oxidation are unusually mild for such a hydrolysis. Convincing evidence was obtained for this reaction course, however: 1. Treatment of 1-chloroisoquinoline with acetic acid and water under conditions identical with those of the oxidation resulted in the formation of a 38% yield of isocarbostyril and the recovery of 52% of the starting material. 2. Treatment of isocarbostyril with a mixture of hydrogen peroxide, hydrochloric acid, and glacial acetic acid produced 4-chloroisocarbostyril rapidly in 87% yield. 3. Prolonged treatment of 1-chloroisoquinoline with acetic acid and water at the reaction temperature before addition of the hydrogen peroxide resulted in an increased yield of 4-chloroisocarbostyril. 4. Addition of bromide ion to a 1-chloroisoquinoline-oxidation mixture resulted in the formation of 4-bromoisocarbostyril.

EXPERIMENTAL[8,9]

4-Chloroisocarbostyril. A mixture of 1.64 g. of 1-chloroisoquinoline,[5] 1 ml. of 30% hydrogen peroxide, and 3 ml. of glacial acetic acid was heated at 65° for a period of 12 hr., 0.8 ml. more hydrogen peroxide being added after 3 hr. The reddish solution, from which crystals separated during the

(1) This investigation was supported in part by a research grant, number C-2574, from the National Cancer Institute of the National Institutes of Health, Public Health Service.

(2) M. M. Robison and B. L. Robison, *J. Org. Chem.*, **21**, 1337 (1956).

(3) M. M. Robison and B. L. Robison, *J. Am. Chem. Soc.*, in press.

(4) E. Shaw, J. Bernstein, K. Losee, and W. A. Lott, *J. Am. Chem. Soc.*, **72**, 4362 (1950).

(5) S. Gabriel and J. Colman, *Ber.*, **33**, 980 (1900).

(6) Cf. S. Gabriel, *Ber.*, **18**, 3470 (1885) for the corresponding reaction with 3-phenylisocarbostyril.

(7) Cf. W. J. Gensler in *Heterocyclic Compounds*, R. C. Elderfield ed., John Wiley and Sons, Inc., New York, N. Y., 1952, Vol. 4, p. 421.

(8) Melting points are corrected.

(9) Analyses by Weiler and Strauss, Oxford, England, and by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y., except for some nitrogen analyses which were carried out by a semimicro Kjeldahl technique in this laboratory.

heating period, was evaporated to dryness *in vacuo*, water was added, and the evaporation was repeated to yield a mixture of red solid and brown tar. This was washed well with ethanol to remove the tarry material and the residue was dissolved as completely as possible in about 15 ml. of boiling butyl acetate (Darco). From the cooled filtrate 4-chloroisocarbostyril was deposited, in yields averaging 20–24%. The analytical sample was prepared by additional recrystallizations from butyl acetate, from benzene, and from acetic acid–water; white needles, m.p. 235.5–237.5° dec.

Anal. Calcd. for C_9H_6NOCl: C, 60.18; H, 3.37; N, 7.80 Found: C, 60.57; H, 3.61; N, 7.60.

The infrared spectrum showed carbonyl absorption at 1680 cm.$^{-1}$ and an additional band at 1650 cm.$^{-1}$ In addition, the usual bands ascribed to ring absorption[2] were observed at 1625 cm.$^{-1}$ and 1600 cm.$^{-1}$

When the reaction was carried out with twice as much acetic acid at steam bath temperature for 6 hr., without the second addition of peroxide, a typical yield of recrystallized product was 38%. When a reaction mixture was prepared as in the first method, but with water instead of hydrogen peroxide, and heated at 65° for 20 hr., further heating and peroxide additions by the usual procedure afforded a 40.5% yield of recrystallized product.

The chloroisocarbostyril was also prepared from a mixture of 1.45 g. of isocarbostyril, 1 ml. of 30% hydrogen peroxide, 3 ml. of glacial acetic acid, and 0.84 ml. of concentrated hydrochloric acid. On gentle warming a vigorous reaction ensued and occasional cooling was necessary for the first hour. After a final period of heating for 1 hr. at 65°, the mixture was cooled and an 87% yield of pale, orange needles, m.p. 230–236.5° dec., was separated. Recrystallization from butyl acetate (Darco) afforded white needles, m.p. 236–238° dec., in 66% yield.

Hydrolysis of 1-chloroisoquinoline. When 0.33 g. of the chloro compound was treated as in the oxidations, except that water was substituted for hydrogen peroxide, an oily solid was obtained on evaporation of most of the solvent. This was washed with warm water and with ether to leave 0.11 g. of undissolved isocarbostyril, m.p. 203–206.5°, undepressed on admixture with an authentic sample. From the filtrate a 52% yield of unchanged starting material was obtained by extraction with ether and evaporation. This had m.p. 33.5–36.5° both alone and on admixture with 1-chloroisoquinoline.

N-Acetyl-4-chloroisocarbostyril. A mixture of 1.35 g. of 4-chloroisocarbostyril and 11 ml. of acetic anhydride was refluxed for 5.5 hr., then cooled to deposit a 62% yield of long, white needles of the acetyl derivative, m.p. 105–107.5°. Evaporation of the anhydride to dryness *in vacuo* afforded an additional 36% of less pure tan solid. The analytical sample, which was recrystallized from hexane, had m.p. 105.5–107°. The compound is formulated as *N*-acetyl-4-chloroisocarbostyril, rather than as the 1-acetoxy compound, on the basis of infrared absorptions at 1723 cm.$^{-1}$ and 1685 cm.$^{-1}$ and ring absorptions at 1625 cm.$^{-1}$ and 1595 cm.$^{-1}$ A similar situation obtains with acyl derivatives of isocarbostyril.[2]

Anal. Calcd. for $C_{11}H_8NO_2Cl$: C, 59.61; H, 3.64; N, 6.32; Cl, 16.00. Found: C, 59.81; H, 3.64; N, 6.39; Cl, 15.75.

When the acetyl derivative was hydrolyzed in refluxing 10% hydrochloric acid, it was converted to 4-chloroisocarbostyril in essentially quantitative yield.

Hydrogenolysis of 4-chloroisocarbostyril. A mixture of 135 mg. of the chloro derivative, 0.1 g. of 5% palladium-on-charcoal, 0.3 g. of potassium acetate, and 20 ml. of 95% ethanol was stirred with hydrogen until slightly more than the theoretical volume had been absorbed. The catalyst was separated and the solution evaporated to dryness *in vacuo*. The isocarbostyril, after washing with water, weighed 71 mg. (65%) and had m.p. 202.5–205.5°, undepressed on admixture with the known compound.

1,4-Dichloroisoquinoline. When 0.01 mole of the chloroisocarbostyril was heated with 6 ml. of phosphorus oxychloride in a sealed tube at 120° for 4 hr., and the mixture poured onto ice, a quantitative yield of 1,4-dichloroisoquinoline, m.p 93–94°, separated. Steam-distillation and recrystallizations from ethanol-water produced the analytical sample, long, white needles, m.p. 92–92.5° (reported[5] m.p. 88–89°).

Anal. Calcd. for $C_9H_5NCl_2$: C, 54.58; H, 2.54; N, 7.07. Found: C, 54.65; H, 2.92; N, 7.04.

The melting point was undepressed on admixture with an authentic sample prepared by the method of Gabriel.[5] A preparation more convenient than the latter involved heating a mixture of 2.90 g. of isocarbostyril and 7 g. of phosphorus pentachloride at 140° for 6 hr. The mixture was poured onto ice and the crude product recrystallized from ethanol-water; yield 50%, m.p. 92–94°.

Independent preparation of 4-chloroisocarbostyril. A solution of 1 g. of sodium and 0.6 g. of the dichloro compound in 15 ml. of methanol was heated in a sealed tube at 100° for 1.5 hr. The solvent was evaporated and the residue was washed with water to produce the crude methyl ether, m.p. 48–50°. This was not investigated further but was heated in a sealed tube with 6 ml. of concentrated hydrochloric acid at steam bath temperature for 2 hr. Addition of water allowed the separation of 4-chloroisocarbostyril, m.p. 238–238.5° dec., undepressed on admixture with material from the oxidation. The infrared spectra of the two samples were also identical. The over-all yield was 91%.

4-Bromoisocarbostyril. A mixture of 1.45 g. of isocarbostyril, 1 ml. of 30% hydrogen peroxide, and 3 ml. of glacial acetic acid was maintained at 20–25° while a solution of 1.69 g. of 48% hydrobromic acid in 1 ml. of acetic acid was added dropwise. The mixture was allowed to stand for 3 hr., then heated to 40° for 1 hr. Dilution with water afforded a 78% yield of crude 4-bromo compound, m.p. 233–237° dec. The analytical sample was recrystallized from benzene, from butyl acetate, and from 1:1 acetic acid–water; m.p. 248–249° dec.

Anal. Calcd. for C_9H_6NOBr: N, 6.25. Found: N, 6.18.

The substance was also obtained when one equivalent of potassium bromide was added to a 1-chloroisoquinoline–oxidation mixture. Initial cooling was necessary. The reaction mixture was worked up in the usual manner to produce the crude bromo compound in approximately 7% yield. After two recrystallizations the material melted at 246–248° dec.

Absorption spectra. Infrared spectra were determined with either a Perkin-Elmer or Baird spectrophotometer (KBr disk) by Dr. S. M. Nagy and associates at the Massachusetts Institute of Technology.

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Reactions of Alkyl Phosphites with Diethyl Azodicarboxylate[1]

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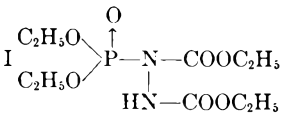
The reaction of diethyl phosphite with azodicarboxylic acid diethyl ester under alkaline catalysis was studied in the hope that the phosphite would add to the double bond of the azo group, forming a phosphoric hydrazide compound. This appeared to take place and a product was isolated which gave

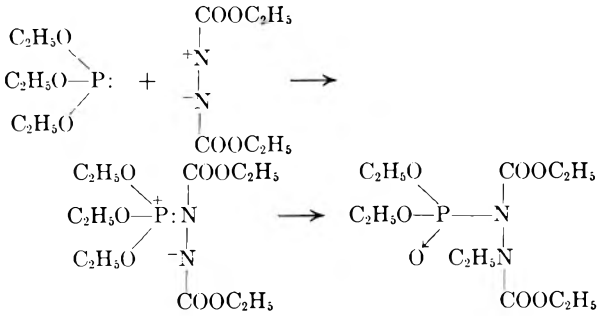
(1) The work described in this paper was carried out under a research grant (Nos. C-327 and CY-2195) to D. M. Greenberg, from the National Cancer Institute, United States Public Health Service.

analytical values for a 1:1 adduct. It may be named diethyl phosphoric acid 1,2-dicarbethoxy hydrazide (I).



The preparative reaction is then analogous to the addition of other active hydrogen compounds to the azo ester double bond[2,3] and to the addition of dialkyl phosphites to the reactive double bond of substituted acrylic esters.[4,5] The product is a very viscous water-soluble oil. In ether solution, it reacted with sodium, evolving hydrogen. This is taken to be evidence for an NH bond, as would be required by the structure. Acid degradation of the compound gave phosphoric acid and ethyl hydrazodicarboxyate together with traces of hydrazine. The isolation of these products also supports the structure I.

Triethyl phosphite was also found to react readily with diethyl azodicarboxylate in ether solution. In this case, no catalyst was necessary and the reaction was extremely vigorous. The product was isolated by evaporation and distillation and was a somewhat more mobile oil than the product formed from diethyl phosphite. The nature of this substance is uncertain, but it is thought that the following is a rational explanation of the reaction. Polarization of the azo group may allow the positive nitrogen atom to react with the electron pair of the phosphite. The transition complex would then decompose by transference of an ethyl group from oxygen to nitrogen as shown:



The change would be analogous to the Arbuzov rearrangement but would be intramolecular, without the usual loss of alkyl halide or equivalent. The postulated reaction product would be an ethyl derivative of the substance formed by the reaction of diethyl phosphite with the azo ester. Acid cleavage of the addition product gave phosphoric acid together with unknown substances. Trimethyl phosphite formed a similar compound with the azo ester but it was not obtained analytically pure.

The reaction of triphenyl phosphite with azodicarboxylic ester occurs slowly at steam bath temperatures. The orange azo color disappears but no pure compound was isolated from the oily mixture.

Some preliminary work was done with triphenylphosphine. In ether solution, when the azo ester is added slowly to triphenyl phosphine solution, a white or yellowish-white precipitate is formed which soon becomes resinous and the orange azo color is destroyed. After the ether is decanted and the residue shaken with water, it crystallizes forming triphenylphosphine oxide in good yield. The supernatant probably contains diethyl hydrazodicarboxylate as the other reaction product. The phosphine oxide was confirmed by melting point and mixed melting point. The first formed resinous substance may be an analog of an ylide type compound.

EXPERIMENTAL

The diethyl azodicarboxylate was made by bromine oxidation of the corresponding hydrazo ester according to the directions of Kenner and Stedman.[6] Thiosulfate washing was avoided and several potassium carbonate washings were used instead.

Reaction of diethyl phosphite with ethyl azodicarboxylate. The diethyl phosphite should be freshly distilled before use as its hydrolysis products also react with the azo ester. The two esters did not react in anhydrous ether solution, even on warming. The reaction could be promoted by sodium methoxide but in this case methanol may add to the azo group, so sodium diethyl phosphite was employed instead. A solution was prepared containing 12.72 ml. (0.08 mole) of the azo ester and 10.24 ml. (0.08 mole) of diethyl phosphite in 50 ml. of anhydrous ether. To this was added dropwise, with stirring and cooling, a solution prepared by reaction of 3 ml. of diethyl phosphite with excess sodium in 20 ml. of anhydrous ether. Each drop of solution caused a vigorous reaction, with spattering and boiling of the ether. The addition was continued until the orange color of the ester was decolorized, only part of the catalyst solution being required. The mixture was left 0.5 hr. and 1 ml. of acetic acid added. The solution was now extracted with $^1/_2$ its volume of water and the aqueous phase re-extracted with ether. The combined ether solutions were dried over anhydrous potassium carbonate, the ether was removed, and the residue was pumped under vacuum in a water bath for several hours. The yield of crude ester was 21.7 g. or 87%. The product was distilled at 165–170°/1–2 mm. and then redistilled for analysis; *Anal.* Calcd. for $C_{10}H_{21}N_2PO_7$: C, 38.46; H, 6.73. Found: C, 38.24; H, 6.88. d 1.1412. The ester is an extremely viscous clear, colorless oil. It is completely water soluble. In anhydrous ether, the ester evolved hydrogen when treated with sodium.

Acid cleavage of the ester. A solution of the ester in a large excess of an equi-volume mixture of 9*N* hydrochloric acid and ethanol was left on the steam bath until it had evaporated to dryness. A white crystalline residue was formed which could be recrystallized from water. On purification, it had m.p. 130–132° which corresponds to that for ethyl hydrazodicarboxylate (lit. 130°[7]). This hydrazo ester is known to be very stable towards hydrolysis by strong

(2) O. Diels, *Ber.*, **55**, 1524 (1922).

(3) O. Diels, *Ann.*, **429**, 1 (1922).

(4) A. N. Pudovik, *Zhur. Obshcheĭ. Khim.*, **22**, 473 (1952); *Chem. Abstr.*, **47**, 2687 (1953).

(5) A. N. Pudovik, *Zhur. Obshcheĭ. Khim.*, **22**, 1143 (1952); *Chem. Abstr.*, **47**, 4836 (1953).

(6) G. W. Kenner and R. J. Stedman, *J. Chem. Soc.*, 2089 (1952).

(7) Th. Curtius and K. Heidenreich, *J. Prakt. Chem.*, **52** (**160**), 476 (1895).

acid.[7] The warm aqueous extract from the crystalline residue of hydrazo ester was heated with ammonium molybdate–nitric acid reagent and gave a voluminous yellow precipitate at once, showing the presence of phosphoric acid. The aqueous extract also gave a faint turbidity with saturated aqueous salicylaldehyde, indicating slight cleavage of the hydrazo ester to hydrazine.

Reaction of triethyl phosphite with ethyl azodicarboxylate. In the pure state these react violently so the action was moderated by dilution with anhydrous ether. A solution of 17.1 ml. (0.1 mole) of triethyl phosphite in 50 ml. of anhydrous ether was treated dropwise with 15.9 ml. (0.1 mole) of the azo ester under a reflux system. A few drops of the azo ester were added at first to start the reaction, and as soon as warming occurred, the remaining ester was added at such a rate that gentle refluxing of the ether took place. After the addition, the solution was refluxed for 0.5 hr. and then ether was distilled from the yellowish solution (an excess of the phosphite did not decolorize, even on heating). The residue was distilled at 170–190° at 10 mm. The product weighed 22.3 g. or 65.6%. The forerun contained a pink material which was somewhat difficult to separate from the product. The addition product was redistilled at 175–188°/10 mm. or 140–155°/2 mm. for analysis.

Anal. Calcd. for $C_{12}H_{25}N_2PO_7$ (1:1 adduct): C, 42.35; H, 7.35. Found, Prepn. I: C, 42.61; H, 6.65. Prepn. II: C, 42.80; H, 7.40.

The density of sample II was 1.1413. The product is a colorless oil, more mobile than the reaction product of diethyl phosphite. It forms two layers with water but is soluble in 30–40 volumes of water on stirring. On warming the saturated aqueous solution, the ester precipitates as an oil which redissolves on cooling.

Acid cleavage of the ester. An analytical sample was heated with an excess of concentrated hydrochloric acid on the steam bath for 12 hr. and left to evaporate on the bath to dryness. A water-soluble, very viscous colorless oil was formed. This gave a strong phosphate test with the molybdate reagent but no hydrazo ester or other crystalline material could be isolated. Only a faint turbidity was produced with salicylaldehyde.

The ester also appears to be hydrolyzed by heating for several days with dilute aqueous ammonium hydroxide. Evaporation left a viscous water-soluble sirup from which no crystalline product could be obtained.

The reaction of trimethyl phosphite with the azo ester gave a similar, distillable compound, also accompanied by a pink by-product. Analysis of the purified product for carbon gave values which were slightly higher than the theoretical.

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Isolation of *N*-Methylcytisine from *Ormosia stipitata* Schery

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During the course of a study of the alkaloids of *Ormosia* species, a number of new alkaloids were isolated. Three oxygen-free compounds, ormosinine, ormosanine, and panamine and two minor oxygen-containing bases were found in *Ormosia panamensis*. Seeds of a number of other species (*O. arilensis*, *O. coccinea*, *O. jamaicensis*, *O. macrophylla*, *O. monosperma*, *O. tovarensis*, *O. costulata*, *O. fastigiata*, *O. nobilis*, and *O. xanthocarpa*) were examined by means of paper chromatography of the alkaloid extracts. Three solvent systems were employed. The results indicated that all of the species contained approximately the same alkaloids in varying amounts.[1]

A recent collection of seeds of *O. stipitata* Schery from the province of Chiriqui, Panama, gave quite different data. Paper chromatographic examinations in various solvents revealed the presence of a large amount of one alkaloid with no indication of other bases. This alkaloid showed bright blue fluorescence under ultraviolet light, but none of the alkaloids present in the other species exhibited fluorescence.

An extraction of the seeds and purification of the alkaloid fraction was carried out on a larger scale by usual methods, and a 1.9% yield of crystalline material was obtained. The analytical data fitted the formula $C_{12}H_{16}ON_2$ and the melting point, optical rotation, and infrared spectrum were in agreement with those reported in the literature for *N*-methylcytisine. Further proof of identity was obtained by comparison of the melting point data for the hydrochloride, picrate, and perchlorate of the isolated material with literature values.

N-Methylcytisine was first found in nature by Power and Salway[2] in *Caulophyllum thalictroides* (Berberidaceae) and since then it has been obtained from many Papilionaceae either as the main alkaloid or with a number of others. A yield of the magnitude found here has not been experienced previously.

The presence of *N*-methylcytisine in *O. stipitata* seeds and its absence in the eleven other *Ormosiae* examined raises a doubt as to whether *O. stipitata* has been correctly assigned to the genus *Ormosia*. This question is currently under study by Dr. J. D. Dwyer of the Department of Biology, St. Louis University, and Dr. G. B. Schubert of the U. S. Department of Agriculture.

EXPERIMENTAL[3]

Paper chromatographic examination. A few seeds of *O. stipitata*, collected by Dr. W. H. Holdridge in Chiriqui, Panama, were crushed with a hammer, defatted with hexane, and extracted with methanol. The extract was evaporated and the residue was dissolved in dilute hydrochloric acid. This solution was placed on Whatman #1 paper and subjected to chromatography in four solvent systems. Each system yielded a single well-defined spot detected by its blue fluorescence under UV light or by spraying the paper with Munier-Dragendorf reagent. The R_f values are in Table I.

(1) H. A. Lloyd and E. C. Horning, *J. Am. Chem. Soc.*, **80**, 1506 (1958).

(2) F. B. Power and A. H. Salway, *J. Chem. Soc.*, **103**, 191 (1913).

(3) All melting points were taken on a Kofler stage. Analyses by J. F. Alicino, Metuchen, N. J.

TABLE I

Solvent System	R_f Value
1. *n*-BuOH, HCl, H_2O (100:20:36)	0.33
2. *sec*-BuOH, HCl, H_2O (100:20:36)	0.41
3. *tert*-BuOH, HCl, H_2O (100:10:20)	0.22
4. *n*-PrOH, 1N NH_4OH (5:1)	0.83

Isolation of N-methylcytisine. The ground seeds (240 g.) were extracted with methanol in a Soxhlet extractor. The extract was evaporated and the residue was treated with 10% hydrochloric acid. The acid solution was shaken with methylene chloride to remove lipids; it was then made basic by the addition of solid potassium carbonate and ammonia, and extracted with chloroform until the aqueous layer gave negative alkaloid tests. The chloroform extract was dried and the solvent was removed *in vacuo*. There was obtained 4.5 g. (1.9%) of colorless crystalline material, m.p 137–139.5°. After recrystallization from ethyl acetate–cyclohexane a sample melted at 140–141°, $[\alpha]^{25}_{589}$ −223°, $[\alpha]^{25}_{436}$ −690° (*c*, 0.905, water).

Anal. Calcd. for $C_{12}H_{16}ON_2$: C, 70.56; H, 7.90; N, 13.72; NCH_3, 7.36. Found: C, 70.54; H, 7.87; N, 13.81; NCH_3, 7.19.

The hydrochloride, picrate, and perchlorate were prepared by standard methods. The melting points are given in Table II.

TABLE II

N-METHYLCYTISINE DATA

			Lit. Values
Base	m.p.	140–141°	138°[2,4]
	$[\alpha]^{25}_{589}$ (water)	−223°	−221.6°[2]
Hydrochloride	m.p.	255–258°	250–255°[2]
Picrate	m.p.	232°(dec.)	234°[4]
Perchlorate	m.p.	277–281°	282°[4]

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(4) L. Marion and J. Ouellet, *J. Am. Chem. Soc.*, **70**, 691 (1948).

11-Alkylated Steroids. II. 11-Methyl-3,11,20-trioxygenated Pregnanes

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Despite the fact that 11-oxosteroids have, on a number of occasions,[1] been treated with organometallic reagents that effected transformations elsewhere in the molecule, reaction at the 11-oxo group has been reported only recently.[2]

We wished to extend our knowledge of 11-methylsteroids, particularly of the pregnane series, and accordingly have prepared several new members of this group.

5β-Pregnane-3,11,20-trione 3,20-bis(ethylene acetal)[3] (IIa) underwent addition of methyllithium smoothly in good yield to give the bisketal IIIa, which, being somewhat difficult to crystallize, was usually not isolated but was hydrolyzed directly to 11β-hydroxy-11-methyl-5β-pregnane-3,20-dione (Va), obtained in 65% yield from IIa. Similarly the hitherto unknown 5α-pregnane-3,11,20-trione 3,20-bis(ethylene acetal) (IIb) was treated with methyllithium to give the crystalline bisketal IIIb in 82% yield. Hydrolysis of IIIb afforded 11β-hydroxy-11-methyl-5α-pregnane-3,20-dione (Vb) in 80% yield. Apparently the configuration of the molecule at C-5 has little or no effect on the addition reaction at the 11-oxo group.

In the first paper in this series,[2] it was pointed out that although 21-triphenylmethoxypregna-5,-17(20)-[cis]-diene-3,11-dione 3-ethylene acetal underwent addition of methyllithium to the 11-oxo group, neither 21-hydroxypregna-5,17(20)-[cis]-diene-3,11-dione 3-ethylene acetal nor its acetate could be converted to the 11-methylated derivative. This was felt to be caused by initial formation of the 21-alcohol lithium salt, which might then be expected to be resistant to further attack by methyllithium. The adverse effect of the hydroxyl group (or of a group readily converted to hydroxyl by methyllithium) seemed clear. However, we have now found that in at least one case where the molecule contains a free hydroxyl group, namely 3α-hydroxy-5β-pregnane-11,20-dione 20-ethylene acetal[3] (VII), addition of methyllithium to the 11-oxo group does take place. Subsequent acid hydrolysis of the product gave 3α,11β-dihydroxy-11-methyl-5β-pregnan-20-one (VIIIa), which was also prepared by selective sodium borohydride reduction[4] of 11β-hydroxy-11-methyl-5β-pregnane-3,20-dione (Va).

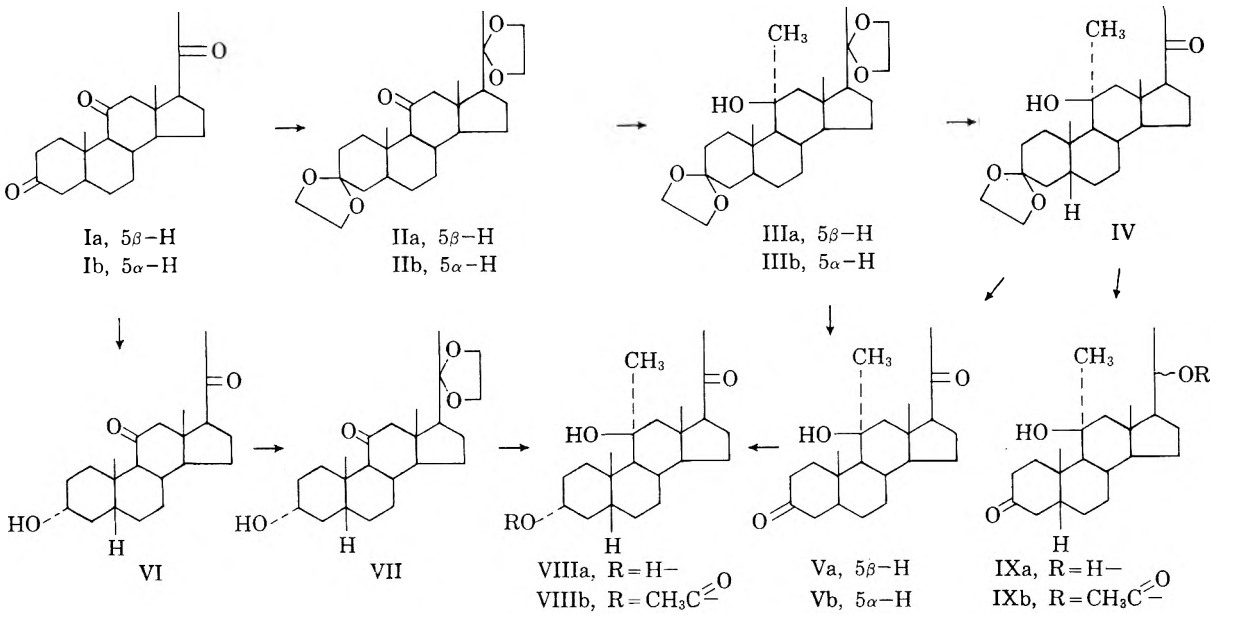
In connection with the preparation of Va, it was possible to isolate a second substance by chromatography of the total crude acid hydrolysis product. This material appeared, in the basis of analytical data, to be a monoacetal. In order to determine which ketone group was protected, the material was reduced with sodium borohydride and then subjected to acid hydrolysis. The resultant diol IXa could not be crystallized but was converted to the crystalline acetate IXb, which was not identical with the acetate (VIIIb) of 3α,11β-dihydroxy-11-methyl-5β-pregnan-20-one (VIIIa). Accordingly, IXb must have been a 20-acetoxy compound, de-

(1) See, for example: R. B. Turner, V. R. Mattox, L. L. Engel, B. F. McKenzie, and E. C. Kendall, *J. Biol. Chem.*, **166**, 345 (1946); A. Wettstein and C. Meystre, *Helv. Chim. Acta*, **30**, 1262 (1947); V. R. Mattox and E. C. Kendall, *J. Biol. Chem.*, **185**, 589 (1950).

(2) G. S. Fonken and J. A. Hogg, *Tetrahedron*, **2**, 365, (1958).

(3) E. P. Oliveto, T. Clayton, and E. B. Hershberg, *J. Am. Chem. Soc.*, **75**, 486 (1953).

(4) E. R. Garrett and D. A. Lyttle, *J. Am. Chem. Soc.*, **75**, 6051 (1953).



rived from 11β-hydroxy-11-methyl-5β-pregnane-3,20-dione 3-ethylene acetal (IV).

In this series of compounds, the carbonyl absorption maxima in the infrared spectra of Nujol mulls showed consistently different frequencies for 3- or 20-ketones. Compounds IV, VIIIa, and VIIIb, having a 20-ketone, showed a carbonyl absorption at 1682–1687 cm.$^{-1}$, whereas compound IXb, with a 3-ketone, absorbed at 1707 cm.$^{-1}$ Compounds Va and Vb, having both 3- and 20-ketones, showed two maxima, the former at 1715 and 1687 cm.$^{-1}$, and the latter at 1706 and 1681 cm.$^{-1}$ These facts serve as additional evidence of the structure of the monoketal IV.

EXPERIMENTAL[5]

5α-Pregnane-3,11,20-trione 3,20-bis(ethylene acetal) (IIb). A mixture of 22 g. of 5α-pregnane-3,11,20-trione (Ib), 100 ml. of ethylene glycol, 5 g. of *p*-toluenesulfonic acid monohydrate, and 500 ml. of toluene was stirred and refluxed through a Dean-Stark water trap for about 24 hr. and then cooled to 25°. A solution of 5 g. of potassium hydroxide in 50 ml. of methanol was added, and the mixture was washed with four 1-l. portions of water. The organic solution was filtered through a short column (5.5 × 15 cm.) of Florisil topped with sodium sulfate, "elution" being effected with 3 l. of benzene. Evaporation of the "eluate" gave a solid which was recrystallized from about 2 l. of Skellysolve B to give 14.99 g. of 5α-pregnane-3,11,20-trione 3,20-bis(ethylene acetal) (IIb), m.p. 207–210°, $[\alpha]_D$ + 48° (acetone), γ_{max}^{Nujol} 1693 (C=O), 1127, 1094, 1067, 1052, 1030 (C—O).

Anal. Calcd. for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15. Found: C, 71.53; H, 9.26.

11β-Hydroxy-11-methyl-5α-pregnane-3,20-dione (Vb). A solution of 10 g. of 5α-pregnane-3,11,20-trione 3,20-bis(ethylene acetal) (IIb) in 150 ml. of benzene and 100 ml. of ether was treated with a threefold molar excess of approximately molar ethereal methyllithium and allowed to stand at room temperature overnight. The mixture was washed twice with water, the organic phase filtered through sodium sulfate, and evaporated to dryness. The residue was crystallized from Skellysolve B to give 8.5 g. of *11β-hydroxy-11-methyl-5α-pregnane-3,20-dione bis(ethylene acetal)* (IIIb) m.p. 131–133°. For analysis a 150 mg. sample was recrystallized again from Skellysolve B to m.p. 135–136°, $[\alpha]_D$ + 27° (acetone), γ_{max}^{Nujol} 3610 (OH; very weak), 1183, 1164, 1126, 1096, 1076, 1054, 1031 (C—O).

Anal. Calcd. for $C_{26}H_{42}O_5$: C, 71.85; H, 9.74. Found: C, 71.74; H, 9.89.

The remaining IIIb was dissolved in 150 ml. of hot methanol, cooled to room temperature, and treated with 10 ml. of 3*N* sulfuric acid overnight. Crystallization of the product began spontaneously and was increased by addition of 10 ml. of water. Filtration, with washing of the precipitate successively with water, aqueous 4% sodium bicarbonate, and water, gave 6.51 g. of crude Vb, m.p. 198–212°. Addition of 100 ml. of water to the filtrate gave an additional 1.3 g., m.p. 190–205°. The two crops were combined and recrystallized from acetone, giving 5.1 g. of Vb, m.p. 218–222°. A sample for analysis was recrystallized from acetone to m.p. 223–225°, $[\alpha]_D$ + 101° (acetone), γ_{max}^{Nujol} 3440 (OH), 1706, 1681 (C=O).

Anal. Calcd. for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 76.02; H, 10.12.

11β-Hydroxy-11-methyl-5β-pregnane-3,20-dione bis(ethylene acetal) (IIIa). A solution of 50.9 g. of 5β-pregnane-3,11,-20-trione 3,20-bis(ethylene acetal) (IIa)[3] in 1 l. of 1:1 benzene-ether was treated with 400 ml. of 0.6*M* ethereal methyllithium at room temperature overnight. The reaction mixture was washed thrice with water and the organic phase dried over sodium sulfate and evaporated to dryness. Drying the residue *in vacuo* at 60° gave a colorless glass that crystallized after standing at room temperature for one month. Recrystallization from Skellysolve B afforded 33.5 g. of IIIa, m.p. 95–106°. For analysis a sample was recrystallized four times from Skellysolve B to m.p. 79–83°, $[\alpha]_D$ + 40° (acetone), γ_{max}^{Nujol} 3480 (OH), 1247, 1218, 1183, 1087, 1062, 1052 (C—O).

Anal. Calcd. for $C_{26}H_{42}O_5$: C, 71.85; H, 9.74. Found: C, 72.18; H, 9.77.

The erratic change in melting point on recrystallization, and the poor analysis, suggest that partial ketal cleavage may have taken place during recrystallization of IIIa.

11β-Hydroxy-11-methyl-5β-pregnane-3,20-dione (Va) was prepared as described above from 12.7 g. of IIa. The total crude bisketal IIIa thus obtained was dissolved in 200 ml.

(5) Infrared spectra were measured using a Perkin-Elmer Model 21 Spectrophotometer. Maxima are expressed in cm.$^{-1}$ Rotations were determined in acetone (c ~1%). Melting points, determined on a Fisher-Johns block, are uncorrected.

of hot methanol and treated with 10 ml. of 3*N* sulfuric acid at room temperature for 20 hr. Slow addition of 190 ml. of water, and cooling, precipitated the crude product, which was recovered by filtration, washed with water, and dried. One recrystallization from acetone–Skellysolve B afforded 6.75 g. of Va, m.p. 162–165.5°. A sample for analysis was repeatedly recrystallized from the same solvents to m.p. 171–173°, $[\alpha]_D$ + 106° (acetone), γ_{max}^{Nujol} 3420 (OH), 1715, 1687 (C=O).

Anal. Calcd. for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 76.58; H, 9.98.

Another experiment, carried out as described above, was worked up by extraction with methylene chloride, following dilution of the acid hydrolysis mixture with water. The crude material thus obtained was chromatographed over 350 g. of Florisil. Elution with 5% acetone–methylene chloride afforded about 2.5 g. of crude oil, recrystallized from acetone–Skellysolve B to give 1.18 g. of *11β-hydroxy-11-methyl-5β-pregnane-3,20-dione 3-ethylene acetal* (IV), m.p. 139–142°, γ_{max}^{Nujol} 3420 (OH), 1682 (C=O), 1100, 1087, 1048 (C—O).

Anal. Calcd. for $C_{24}H_{38}O_4$: C, 73.80; H, 9.81. Found: C, 73.62; H, 10.33.

Hydrolysis of 100 mg. of IV in 5 ml. of methanol containing 5 ml. of 0.1*N* sulfuric acid at room temperature overnight afforded, following addition of 4 ml of water, 85 mg. of the dione Va, m.p. 167–168°.

3α,11β-Dihydroxy-11-methyl-5β-pregnan-20-one (VIIIa). *A. By selective reduction*[4] *of* Va. To a solution of 1.9 g. of Va in 10 ml. of purified[6] dioxane, cooled in an ice bath, was added 62 mg. of sodium borohydride in 1 ml. of 0.1*N* sodium hydroxide. The mixture was stirred for 2 min. with cooling, and then diluted slowly (5 min.) with 12 ml. of water, followed by 0.65 ml. of concentrated hydrochloric acid. Further dilution with water and extraction with methylene chloride gave a crude product that was chromatographed over Florisil. Elution with, at first 2% acetone–methylene chloride, and finally, 25% acetone–methylene chloride gave crude VIIIa, recrystallized first from acetone–Skellysolve B and then from ethyl acetate to give 0.93 g. of pure VIIIa, m.p. 181–183°, identical to VIIIa prepared as described below.

B. From 3α-hydroxy-5β-pregnane-11,20-dione (VI). 3α-Hydroxy-5β-pregnane-11,20-dione (VI) was converted to the 20-ethylene acetal (VII),[2] m.p. 139–141°, $[\alpha]_D$ + 55° (acetone).

A solution of 13.6 g. of VII in 150 ml. of benzene and 100 ml. of ether was treated with 144 ml. of *M* ethereal methyllithium at room temperature overnight. The reaction mixture was washed several times with water, the organic phase dried over sodium sulfate, and evaporated to dryness. Attempts to crystallize the resultant glass were unsuccessful, both before and after chromatography over Florisil (the major product was eluted with 5–10% acetone–Skellysolve B, and amounted to about 13 g.), so it was dissolved in 200 ml. of methanol and treated with 10 ml. of 3*N* sulfuric acid at room temperature for 28 hr. Addition of 200 ml. of water, and prolonged cooling at about 5° afforded 6.74 g. of crude crystals, m.p. 149–168°, consisting largely of VIIIa. A sample for analysis was recrystallized repeatedly from acetone–Skellysolve B to m.p. 184–186°, $[\alpha]_D$ + 111° (acetone), γ_{max}^{Nujol} 3540, 3440 (OH), 1687 (C=O).

Anal. Calcd. for $C_{22}H_{36}O_3$: C, 75.81; H, 10.41. Found: C, 75.43; H, 10.25.

The *3-acetate* (VIIIb), prepared by treatment of 200 mg. of VIIIa with 2 ml. of pyridine and 2 ml. of acetic anhydride at room temperature overnight, was obtained in 93% yield, m.p. 169–171.5°. Recrystallization from acetone–Skellysolve B afforded an analytical sample, m.p. 171–172.5°, $[\alpha]_D$ + 112° (acetone), γ_{max}^{Nujol} 3440 (OH), 1725, 1240 (CH_3CO_2), 1684 (C=O).

(6) K. Hess and H. Frahm, *Ber.*, **71**, 2627 (1938).

Anal. Calcd. for $C_{24}H_{38}O_4$: C, 73.80; H, 9.81. Found: C, 73.50; H, 9.61.

11β,20ξ-Dihydroxy-11-methyl-5β-pregnan-3-one (IXa) was obtained by treatment of 500 mg. of the monoketal IV with 122 mg. of sodium borohydride in 10 ml. of methanol at room temperature overnight, followed by hydrolysis of the ketal by addition of 2 ml. of 3*N* sulfuric acid in 5 ml. of methanol. After a 4 hr. hydrolysis, dilution with water and extraction with methylene chloride and eventual evaporation of the solvent gave an oil (IXa) that failed to crystallize even after Florisil chromatography (elution with 10% acetone–Skellysolve B).

Acetylation of the oily IXa with acetic anhydride–pyridine at room temperature gave, after two recrystallizations from acetone–Skellysolve B, the 20ξ-acetate, m.p. 167–169°, $[\alpha]_D$ + 42° (acetone), γ_{max}^{Nujol} 3500 (OH), 1707 (C=O), 1262 (acetate C—O), not identical with VIIIb.

Anal. Calcd. for $C_{24}H_{38}O_4$: C, 73.80; H, 9.81 Found: C, 73.82; H, 9.77.

Acknowledgment. I am indebted to Miss M. A. Scheri for technical assistance, to Mr. W. A. Struck and associates for the microanalyses and optical rotation determinations, and to Dr. J. L. Johnson and associates for the infrared spectra determinations and interpretations.

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2-Fluoro- and 2,2-Difluoroethylnitroguanidine

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The preparation of 2,2,2-trifluoroethylnitroguanidine has been reported.[1] 2-Fluoro- and 2,2-difluoroethylnitroguanidine have now been prepared in a similar manner by the reaction of the respective fluoroethylamines with 1-nitro-2-methyl-2-thiopseudourea. Efforts to nitrate the fluoroalkylnitroguanidines to dinitroguanidine by methods similar to those of McKay and Milks[2] and Meen and Wright[3] were not successful. The nitrate salts of the original fluoroalkylamines were isolated indicating that decomposition had occurred. 2-Fluoroethylnitroguanidine was cyclized to the tetrahydrofluoride salt of 2-imino-1,3-diazacyclopentane. The free base of this compound was identified as the picrate. A comparable cyclization procedure applied to the other fluoroalkylnitroguandiines gave negative results. The nitrate and picrate salts of 2-fluoro- and 2,2-difluoroethylguanidine were prepared from the corresponding fluoroethylnitroguanidines.

(1) V. Milani, S. Skolnik, and R. Evans, *J. Am. Chem. Soc.*, **77**, 2903 (1955).

(2) A. F. McKay and J. E. Milks, *J. Am. Chem. Soc.*, **72**, 1616 (1950).

(3) R. H. Meen and G. F Wright *J. Am. Chem. Soc.*, **74**, 2077 (1952).

EXPERIMENTAL[4]

2-Fluoroethylnitroguanidine. To 4.0 g. (0.0296 mole) of 1-nitro-2-methyl-2-thiopseudourea was added 8.7 g. (0.1382 mole) of 2-fluoroethylamine.[5] An immediate reaction took place which was controlled by cooling with ice. The reaction was maintained at 35–40° for 50 min., cooled to room temperature, 50 ml. of ether added, and the solid was removed by filtration. The precipitate was washed on the filter with three 25-ml. portions of ether. Crystallization from ethanol gave a product which melted at 145–145.5°. The yield based on 1-nitro-2-methyl-2-thiopseudourea was 77.2%.

Anal. Calcd. for $C_3H_7FN_4O_2$: C, 24.00; H, 4.70; N, 37.32. Found: C, 24.40; H, 4.86; N, 36.94.

2-Fluoroethylguanidine picrate. The picrate was prepared by the hydrogenolysis procedure used for the preparation of 2,2,2-trifluoroethylguanidine picrate[1] and melted at 189–191°.

Anal. Calcd. for $C_9H_{11}FN_6O_7$: C, 32.34; H, 3.32; N, 25.15. Found: C, 32.46; H, 3.26; N, 24.70.

2-Fluoroethylguanidine nitrate. This salt was prepared by the method used to prepare 2,2,2-trifluoroethylguanidine nitrate[1] and melted at 104–105°.

Anal. Calcd. for $C_3H_9FN_4O_3$: C, 21.43; H, 5.40; N, 33.33. Found: C, 21.21; H, 5.26; N, 33.13.

2-Imino-1,3-diazacyclopentane tetrahydrofluoride. 2-Fluoroethylnitroguanidine (1.0 g., 0.066 mole) was dissolved in 50 ml. of 1-hexanol and heated at the reflux temperature (157°) for 6 hr. At the end of that time some crystalline material deposited on the side of the flask.

After standing overnight at room temperature, the brown crystalline material was removed, dissolved in hot water, and treated with Norit to remove the color. The Norit was removed, the aqueous solution evaporated to dryness and the residue crystallized from a mixture of ethanol and water. The purified material weighed 0.174 g. An elemental analysis indicated approximately 3.6 molecules of hydrogen fluoride for each molecule of imino compound. After dissolving in 40% aqueous hydrogen fluoride, allowing to stand overnight at room temperature, evaporating to dryness, and crystallizing from an ethanol-water solution, the elemental analysis corresponded to the tetrahydrofluoride salt of 2-imino-1,3-diazacyclopentane and melted at 227–231° dec.

Anal. Calcd. for $C_3H_{11}F_4N_3$: C, 21.82; H, 6.72; N, 25.45. Found: C, 21.37; H, 5.75; N, 25.10.

This compound was converted to the picrate which melted at 221–223°. A mixed melting point with an authentic sample of 2-imino-1,3-diazacyclopentane picrate was not depressed. This picrate also gave the correct elemental analysis.

N-(2,2-Difluoroethyl)-phthalimide. This compound was prepared by a modification of the method of Childs and coworkers.[5] 1,1-Difluoro-2-bromoethane, 6.05 g. (0.0417 mole, 10% excess), 6.966 g. (0.0376 mole) potassium phthalimide and 5 ml. of dimethylformamide were placed in a 22-ml. Parr bomb. The bomb was attached to a horizontal stirring shaft in such a manner that it would rotate end over end inside a furnace. The bomb was rotated and heated at 210° for 8 hr. After cooling, the contents of the bomb were removed, poured into water, and filtered. The precipitate was washed with water, dissolved in hot ethanol, and treated with decolorizing carbon. The carbon was removed and the product crystallized from the ethanol solution. After recrystallization from ethanol the product weighed 3.73 g. (47%) and melted at 116.5–117.5°.

Anal. Calcd. for $C_{10}H_7F_2NO_2$: C, 56.87; H, 3.34; N, 6.63. Found: C, 56.91; H, 3.02; N, 6.56.

2,2-Difluoroethylnitroguanidine. 2,2-Difluoroethylamine (1.897 g., 0.0234 mole), prepared from *N*-(2,2-difluoroethyl)-phthalimide by the method of Childs and co-workers[5] was placed in a 50-ml. flask fitted with a Teflon-coated magnetic stirrer and a reflux condenser. To this was added at once 1.458 g. (0.0108 mole) of 1-nitro-2-methyl-2-thiopseudourea. The flask was then placed in a water bath at 50° and the contents stirred. The reaction was allowed to proceed without heating until at the end of 20 min. the temperature of the bath was 34°. Ethyl ether (10 ml.) was then added through the condenser and the reaction heated at the reflux temperature of the ether for an additional 20 min. The reaction mixture was then cooled, filtered, and the precipitate washed with ether. The product weighed 1.66 g. (91%) and after two crystallizations from ethanol melted at 162.5–163.5°.

Anal. Calcd. for $C_3H_6F_2N_4O_2$: C, 21.43; H, 3.60; N, 33.33. Found: C, 21.66; H, 3.84; N, 33.00.

2,2-Difluoroethylguanidine picrate. The picrate was prepared by the hydrogenolysis procedure used to prepare 2,2,2-trifluoroethylguanidine picrate[1] and melted at 197–198°.

Anal. Calcd. for $C_9H_{10}F_2N_6O_7$: C, 30.69; H, 2.86; N, 23.86. Found: C, 30.88; H, 3.03; N, 23.82.

2,2-Difluoroethylguanidine nitrate. The nitrate salt was prepared from the picrate by the method used to prepare 2,2,2-trifluoroethylguanidine nitrate[1] and melted at 93.0–94.5°.

Anal. Calcd. for $C_3H_5F_2N_4O_3$: C, 19.36; H, 4.33; N, 30.10. Found: C, 19.24; H, 4.45; N, 29.51.

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(4) All melting points were measured on a Kofler micro hot stage.

(5) A. F. Childs, L. J. Goldsworthy, G. F. Harding, F. E. King, A. W. Nineham, W. L. Norris, S. G. P. Plant, B. Shelton, and A. L. L. Tompsett, *J. Chem. Soc.*, 2174 (1948).

Carbonyl Stretching Frequencies of Some Oxalate Esters

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Only a few references indicate the position of the carbonyl stretching frequencies of oxalate esters. Hampton and Newell reported only a single peak for di-*n*-butyl oxalate,[1] at 1746 cm.$^{-1}$ This information led Bellamy to conclude that interaction between adjacent carbonyl groups was small.[2] Miyazawa and Kurantani[3] also reported only a single C=O stretching frequency for dimethyl oxalate, 1730 cm.$^{-1}$ More recently Bender observed two carbonyl stretching frequencies in a spectrum of diethyl oxalate.[4] Our findings also show two carbonyl stretching frequencies in oxalate esters.

(1) R. R. Hampton and J. E. Newell, *Anal. Chem.*, **21**, 914 (1949).

(2) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, J. Wiley, New York, N. Y., 1954, p. 157.

(3) T. Miyazawa and K. Kurantani, *J. Chem. Soc. Japan* (Pure Chemistry Section), **72**, 804 (1951). *Chem. Abstr.*, **47**, 43d (1953).

(4) M. L. Bender, *J. Am. Chem. Soc.*, **75**, 5986 (1953).

EXPERIMENTAL

Ethyl chloroglyoxylate was prepared by the method of Southwick and Seivard[5] in 75.5% yield. Octyl chloroglyoxylate and phenyl chloroglyoxylate were obtained from the reaction of oxalyl chloride and 1-octanol or phenol, respectively.[6] Dioctyl oxalate could be isolated as a high-boiling fraction in the synthesis of octyl chloroglyoxylate. The preparation of hydroquinone bis-ethoxalyl ester illustrates the method used in synthesizing the mixed esters.

Hydroquinone bis-ethoxyalyl ester. A stirred solution of 2.2 g. (0.02 mole) hydroquinone in 25 ml. peroxide-free dioxane[7] was treated with 5.7 g. (0.042 mole) ethyl chloroglyoxylate. The solution was cooled in an ice bath and 5.2 g. (0.04 mole) quinoline[8] was added dropwise. After stirring thirty minutes more in the ice bath, water was added to dissolve the quinoline hydrochloride and precipitate the product. The white crystalline solid was filtered, washed twice with 20 ml. methanol, and dried to yield 2.9 g. hydroquinone bis-ethoxyalyl ester whose m.p., 80–81°,[9] was not changed by recrystallization from methanol.

Anal. Calcd. for $C_{14}H_{14}O_8$: C, 54.2; H, 4.5. Found: C, 54.3; 54.3; H, 4.6, 4.5.[10]

Diethleneglycol bis-ethoxalyl ester. Diethyleneglycol, 7.95 g. (0.075 mole) treated with 21.8 g. (0.16 mole) ethyl chloroglyoxylate and 19.3 g. (0.15 mole) quinoline yielded the diethoxalate, 12.7 g., b.p. 165–172°/0.3 mm.

Anal. Calcd. for $C_{12}H_{18}O_9$: C, 47.1; H, 5.9. Found: C, 47.2; H, 5.8.

Diphenyl oxalate. Phenol, 3.76 g. (0.04 mole), oxalyl chloride, 2.52 g. 1.7 ml. (0.02 mole), and 5.0 g. 2.4 ml. (0.04 mole) quinoline yielded white needles, m.p. 135–137° (hexane).

Anal. Calcd. for $C_{14}H_{10}O_4$: C, 69.4; H, 4.2. Found: C, 69.5; H, 4.3.

Ethyl octyl oxalate was not isolated. The sample used for obtaining the spectrum was prepared by dissolving octyl chloroglyoxylate in chloroform containing ethanol.

Ethyl phenyl oxalate. Phenol, 2.83 g. (0.03 mole), ethyl chloroglyoxylate 4.5 g. (0.032 mole), and 3.87 g. (0.03 mole) quinoline yielded the mixed oxalate, b.p. 97–99°/4 mm.

Octyl chloroglyoxylate. 1-Octanol, 13.0 g. (0.1 mole), was added dropwise with stirring to 12.7 g. (0.01 mole) oxalyl chloride, and the mixture was heated on the steam bath for 3 hr. to drive off hydrogen chloride. Fractionation yielded 15.0 g. octyl chloroglyoxylate, b.p. 117–119°/12 mm. and 2.0 g., b.p. 150–157°/0.6 mm. of *dioctyl oxalate.*

Phenyl chloroglyoxylate.[11] Phenol, 2.82 g. (0.03 mole) in ether was added to an ether solution of 3.2 ml. (0.037 mole) oxalyl chloride and the ether solution was stirred two days at room temperature. Fractionation yielded the chloride, b.p. 87–89°/6 mm., white needles, m.p. 56–57°. (Lit. b.p. 97°/12 mm., m.p. 57°.)

Infrared spectra were obtained using a Perkin-Elmer Model No. 21 Spectrophotometer equipped with a sodium chloride prism. Liquid samples were measured as meniscus layers between sodium chloride disks or in chloroform solution. Concentrations were adjusted empirically to result in 30–50% transmission in the carbonyl band regions. Solid samples were measured in chloroform solution or KBr pellets. The ratio of 0.5 to 1 mg. in 500 mg. KBr gave well defined carbonyl bands.

(5) P. L. Southwick and L. L. Seivard, *J. Am. Chem. Soc.*, **71**, 2532 (1949). The potassium salt was prepared as in L. Claissen, *Ber.*, **24**, 127 (1891).

(6) G. v. Frank and W. Caro, *Ber.*, **63B**, 1532 (1930).

(7) L. F. Fieser, *Experiments in Organic Chemistry*, D. C. Heath and Co., Boston, Mass., 1955, p. 282, Method b.

(8) Freshly distilled from zinc dust.

(9) Melting points are not corrected.

(10) Analyses were done by Dr. C. Fitz, Needham, Mass.

(11) R. Stolle and E. Knebel, *Ber.*, **54**, 1215 (1921).

RESULTS

Table I lists the carbonyl stretching frequencies for the diesters and ester chlorides.

TABLE I

Compound	C=O Frequencies	Medium
Diethyl oxalate	1740, 1765 cm.$^{-1}$	Liquid film
Dioctyl oxalate	1740, 1762	$CHCl_3$ solution
	1743, 1765	Liquid film
Ethyl octyl oxalate	1740, 1763	$CHCl_3$ solution
Diethyleneglycol bis-ethoxalyl ester	1742, 1767	Liquid film
	1744, 1765	$CHCl_3$ solution
Ethyl phenyl oxalate	1748, 1775	Liquid film
Hydroquinone bis-ethoxyalyl ester	1752, 1775	KBr pellet
	1751, 1778	$CHCl_3$ solution
Diphenyl oxalate	1758, 1775–1780	KBr pellet
	1760, 1787	$CHCl_3$ solution
Ethyl chloroglyoxylate	1757, 1793	Liquid film
Phenyl chloroglyoxylate	1770, 1785	CCl_4 solution
Octyl chloroglyoxylate	1762, 1795	Liquid film

Two strong intensity peaks attributed to carbonyl stretching are present in every compound examined. The four dialkyl oxalates of this study absorb at 1740–1744 cm.$^{-1}$ and 1762–1767 cm.$^{-1}$ in either liquid phase or chloroform solution. Both peaks of the two alkyl aryl oxalates are at higher frequency, 1748–1752 and 1775–1778 cm.$^{-1}$ while the peaks of diphenyl oxalate are at still slightly higher frequency, 1757–1760 and 1775–1787 cm.$^{-1}$ The two alkyl chloroglyoxylates peak at 1757–1762 and 1793–1795 cm.$^{-1}$ while phenyl chloroglyoxylate absorbs at 1770 and 1785 cm.$^{-1}$ The peak at lower frequency is a little stronger except in the spectra of diphenyl oxalate in chloroform and octyl chloroglyoxylate where the higher frequency band is the stronger.

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A Simple Method for the Preparation of Diethyl Carbonate-(carbonyl-C^{14}) from Barium Carbonate-C^{14}

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Diethyl carbonate-(carbonyl-C^{14}) was required in connection with other work being carried out in this laboratory. Eisenhauer and his co-workers[1] have synthesized this ester according to the method of de Clermont[2] by heating ethyl iodide and silver carbonate-C^{14}. They obtained a 9% yield by the original procedure, but they were able to improve

(1) H. R. Eisenhauer, J. M. Pepper, L. B. Jaques, and J. W. T. Spinks, *Can. J. Chem.*, **30**, 245 (1952).

(2) P. de Clermont, *Ann.*, **91**, 375 (1854); *Ann. chim et phys.*, [3] **44**, 330 (1855).

the yield up to 30% by carrying out the reaction in the presence of a catalytic amount of triethylamine or pyridine under refluxing conditions. In their synthesis, labeled silver carbonate was prepared from sodium carbonate-C^{14}, which in turn was obtained by liberation of carbon dioxide from barium carbonate-C^{14} followed by absorption in sodium hydroxide solution.

We have now found that silver carbonate is obtained in about 90% yield by stirring barium carbonate with aqueous silver nitrate. This simplified the whole procedure very much by eliminating the need of intermediate preparation of labeled sodium carbonate. Silver carbonate and excess of ethyl iodide in dry ether at room temperature in the dark gave diethyl carbonate in about 40% yield based on the barium carbonate used.

EXPERIMENTAL

Silver carbonate-C^{14}. Since silver carbonate is unstable in the light and darkens when exposed even to diffuse room light for several hours, it had to be prepared and handled in the dark. Silver nitrate (4.3 g.) in 10 cc. of water was added gradually to a stirred suspension of 2.473 g. of barium carbonate-C^{14} (0.0538 ± 0.0006 mc./mole) in 10 cc. of water. After stirring for 30 min., the pale yellow precipitate formed was filtered off with a sintered-glass filter, and washed with water until silver ion was no more detected, then with ethanol, and finally with dry ether. The dried material weighed 3.4 g. In a preliminary experiment with ordinary barium carbonate, silver carbonate prepared was analyzed for silver by dissolving it in dilute nitric acid followed by precipitation and weighing of silver chloride (Found: Ag, 70.60. Calcd. for Ag_2CO_3: Ag, 78.23).

Diethyl carbonate-(carbonyl-C^{14}). Silver carbonate-C^{14} (3.4 g.), 5.0 g. of ethyl iodide, and 20 cc. of ether were placed in a 100-cc. Erlenmeyer flask, and the mixture was allowed to stand for 50 hr. in the dark with occasional agitation. It was, after addition of 1.405 g. of non-labeled diethyl carbonate, filtered with a sintered-glass filter, and the residue was washed with two portions of 10 cc. of ether. The filtrate and washings were combined and distilled through a Vigreux column, yielding 1.8 g. of diethyl carbonate-(carbonyl-C^{14}), b.p. 122–126°.

A half gram of the diluted labeled ester obtained above and 0.7 g. of hydrazine hydrate were heated at 120° for 6 hr. in an oil bath. The solid precipitate, on 3 crystallizations from ethanol, gave carbohydrazide-C^{14} of a constant activity of 0.0167 ± 0.0006 mc./mole, m.p. 152.0–152.5°. The diluted ester, therefore, had an activity of 0.0167 mc/mole, and this value indicated that 0.630 g. of diethyl carbonate-(carbonyl-C^{14}) had been formed before the dilution corresponding to a yield of 42.8% based on the barium carbonate-C^{14} used. The total recovery of radioactivity in the product from the active barium carbonate was 37.9%.

Radioactivity determinations. The carbohydrazide-C^{14} (40 mg.) was oxidized according to the method of Van Slyke and Folch,[3] and the liberated carbon dioxide was converted into barium carbonate and counted on an "infinitely thick" layer with an end-window Geiger-Müller counter. The count was corrected for background and compared with a standard barium carbonate-C^{14} of a known activity.

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(3) D. D. Van Slyke and J. Folch, *J. Biol. Chem.*, **136**, 509 (1940).

Further Experiments on the Alkylation of Benzene with C^{14}-Labeled Ethyl Chloride

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In a previous paper,[2] we reported alkylation of benzene with C^{14}-labeled ethyl chloride and aluminum chloride in which no isomerization of the ethyl group occurred. We also found that C^{14}-labeled ethyl chloride was extensively isomerized by treatment with aluminum chloride in the absence of benzene. The latter result raised the question of why no isomerization of the ethyl group occurred during the alkylation, since the two processes probably involve the same intermediate, whether it is a carbonium ion[3] or a complex.[4]

We have now carried out further experiments with C^{14}-labeled ethyl chloride with the aim of learning more about the relationship of isomerization and alkylation. In the previous work,[2] ethyl-2-C^{14} chloride was mixed with aluminum chloride and kept at room temperature for one hour. In two experiments, the degree of isomerization was found to be 84% and 92%, respectively. In order to obtain a better estimate of the rate of the isomerization, we have now allowed ethyl-1-C^{14} chloride to stand over aluminum chloride for *six minutes* and then determined the extent of isomerization as before by recovering the ethyl chloride and adding it to benzene in the presence of fresh aluminum chloride. The ethylbenzene produced was found to contain all the C^{14} in the α-position, hence no detectable isomerization of ethyl-1-C^{14} chloride occurred in six minutes. One may estimate that the rate of isomerization of ethyl-1-C^{14} chloride by aluminum chloride is probably faster but of the same order of magnitude as the rate of isomerization of ethyl-1-C^{14} bromide by aluminum bromide;[5] however, the former system is heterogeneous and the latter is homogeneous, so comparison is difficult.

Assuming that the same intermediate is involved in isomerization and alkylation, the fact that no isomerization was observed when alkylation with labeled ethyl chloride was carried out at 80° may be attributed to the fact that the intermediate reacted with benzene much faster than it underwent

(1) Taken from the M.A. thesis of Stellakis G. Panayides, University of Texas, 1957.

(2) R. M. Roberts, G. A. Ropp, and O. K. Neville, *J. Am. Chem. Soc.*, **77**, 1764 (1955).

(3) (a) C. C. Price, *Org. Reactions*, Vol. III, 7 (1946); (b) L. M. Nash, T. I. Taylor, and W. v. E. Doering, *J. Am. Chem. Soc.*, **71**, 1516 (1949).

(4) H. C. Brown and W. J. Wallace, *J. Am. Chem. Soc.*, **75**, 6279 (1953).

(5) F. L. J. Sixma and H. Hendriks, *Rec. trav. chim.*, **75**, 169 (1956), reported that at 25° the isomerization of ethyl-1-C^{14} bromide containing 0.045 mole aluminum bromide per mole of organic halide was 63% complete in 48 hr.

rearrangement.[2] This seems reasonable since the rate of isomerization of ethyl-1-C^{14} bromide is much slower than that of *n*-propyl bromide,[4,5] whereas the rates of alkylation of benzene by ethyl and *n*-propyl halides must not be very different. Support for this viewpoint of competition between alkylation and isomerization has recently been afforded by the very interesting work of Baddeley and Williamson.[6] We hoped that lowering the temperature at which labeled ethyl chloride was allowed to react with benzene might result in reducing the rate of alkylation more extensively than the rate of isomerization, so that alkylation *with rearrangement* might be observed. For this reason, alkylation of benzene with ethyl-1-C^{14} chloride at room temperature was carried out, using other conditions and amounts exactly as in the previous experiments. The ethylbenzene and diethylbenzene produced were separated by fractional distillation and degraded to benzoic acid and phthalic acid, respectively. Radioassay of these acids showed that 96% of the C^{14} was in the α-positions of the side chains. This corresponded to 4% isotopic rearrangement accompanying the alkylation.

A second experiment was carried out which was identical with this one except that ten times as much aluminum chloride was used. The ethylbenzene and diethylbenzene were distilled as before; degradation gave benzoic acid and phthalic acid which contained only 92% of the C^{14} in the α-positions of the side chains, corresponding to 8% isotopic rearrangement. Although the extent of rearrangement was small in both alkylations, it was well outside the range of the experimental error (*ca.* 1%) and the close agreement of the molecular activity *per ethyl group* in the benzoic acid and phthalic acid assays attested to the reality of the rearrangement.

EXPERIMENTAL

Synthesis of ethyl-1-C^{14} chloride. Acetic-1-C^{14} acid was prepared from methylmagnesium iodide and $BaC^{14}O_3$ ("diluted" with Na_2CO_3) using essentially the method of Spector,[7] modified to a scale of 1 millimole of carbonate. The acetic-1-C^{14} acid was extracted from aqueous solution into ether in a continuous liquid-liquid extractor and the ether solution was dried first over calcium chloride and then over magnesium sulfate. After some of the ether had been removed by distillation, the remaining solution was added to an ether solution of lithium aluminum hydride. (Ordinary acetic acid was added in known amount before the continuous ether extraction and just before the reduction reaction in order to dilute the radioactive material and thus avoid handling losses.) The reaction mixture was stirred at room temperature for 13 hr. and then decomposed with water and dilute sulfuric acid. The ether was removed by distillation through a 50-cm. glass helix-packed column, and ethyl-1-C^{14} alcohol was distilled through the same column. Three portions of ordinary ethyl alcohol were added to the residual aqueous solution and distilled through the column to scavenge all of the radioactive alcohol.

The ethyl-1-C^{14} alcohol was radioassayed in the form of its 3,5-dinitrobenzoate.[8] This derivative was first recrystallized from ethyl alcohol, but progressive loss of radioactivity with each recrystallization was observed. This was undoubtedly due to replacement of the active alcohol group in the ester by inactive groups from the solvent. Substitution of Skellysolve B for alcohol in the recrystallization avoided this complication. From 46.8 mg. of $BaC^{14}O_3$ (6.50 mc./m. mole) there was obtained 31 ml. of ethyl-1-C^{14} alcohol (1.74 μc./m. mole); this corresponded to a radiochemical yield of 59%.

Ethyl-1-C^{14} chloride was prepared from ethyl-1-C^{14} alcohol by treatment with aluminum chloride.[9] This was found to be much easier to control than the reaction with phosphorus pentachloride which was used previously.[2] The product was radioassayed in the form of its mercuric chloride derivative,[10] which was purified by recrystallization from 60% ethyl alcohol.

Radioassays were made by means of wet-oxidation and vibrating-reed electrometry as described previously.[11]

Treatment of ethyl-1-C^{14} chloride with aluminum chloride for 6 min. A 15-ml. (at 0° C.) portion of ethyl-1-C^{14} chloride was transferred in a vacuum line onto 2 g. of solid aluminum chloride. The mixture was quickly brought to room temperature and atmospheric pressure and allowed to stand 6 min. At the end of this time the product was passed through an Ascarite trap to remove hydrogen chloride, a bromine water trap to remove ethylene, and two drying tubes containing, respectively, calcium chloride and magnesium sulfate. The ethyl chloride recovered amounted to 11 ml. (at 0° C.). A 1-ml. sample was converted to the mercuric chloride derivative and radioassayed; 0.524 μc./m. mole.

The remaining 10 ml. of ethyl chloride was dissolved in 31 ml. of cold dry benzene and the solution was added dropwise to a stirred mixture of 1.5 g. of aluminum chloride and 24 ml. of dry benzene heated on a steam cone. Heating and stirring were continued for 1.25 hr. and the reaction mixture was decomposed with ice water and worked up in the usual way. By distillation through a 50-cm. glass helix-packed column there was obtained 4.3 g. of ethylbenzene, b.p. 133–136°. A 1-ml. sample was oxidized by permanganate to benzoic acid. It was found that satisfactory yields could be obtained without resorting to the bromination used previously[2] if the following procedure was followed. In a 150-ml. flask equipped with a reflux condenser and a magnetic stirrer was placed 1 ml. of ethylbenzene, 2 g. of potassium permanganate, and 30 ml. of water. The mixture was heated to gentle reflux and stirred until the permanganate color disappeared; then another 2 g. of permanganate was added. Five grams of permanganate were decolorized in this way and heating and stirring were continued for a total of 30 hr. The mixture was filtered, the manganese dioxide was washed with hot water, the washings were added to the filtrate, and the combined filtrate was extracted with two 10-ml. portions of ether. The aqueous solution was heated to boiling and acidified with hydrochloric acid. The benzoic acid was filtered from the cooled solution and recrystallized from 50% ethyl alcohol; 542 mg., m. p. 120.5–121°. Radioassay of an 8.3-mg. sample gave 0.522 μc./m. mole. The benzoic acid was sublimed and reassayed (6.9 mg.); 0.523 μc./m. mole. The radioactivity of the benzoic acid was thus the same as

(6) G. Baddeley and R. Williamson, *J. Chem. Soc.*, 4647 (1956).

(7) L. B. Spector, Atomic Energy Commission, MDDC 532; *cf.* M. Calvin *et al.*, *Isotopic Carbon*, John Wiley and Sons, Inc., New York, N. Y., 1949, p. 177.

(8) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *The Systematic Identification of Organic Compounds*, Fourth Edition, John Wiley and Sons, Inc., New York, N. Y., 1956, p. 212.

(9) J. F. Norris and B. M. Sturgis, *J. Am. Chem. Soc.*, **61**, 1413 (1939).

(10) Ref. 8, p. 244.

(11) R. M. Roberts and S. G. Brandenberger. *J. Am. Chem. Soc.* **79**, 5484 (1957).

that of the ethyl-1-C^{14} chloride, hence all the C^{14} was in the α-position and no isomerization of the ethyl-1-C^{14} benzene occurred before or during alkylation.

Alkylation of benzene at room temperature by ethyl-1-C^{14} chloride. A mixture of 1.5 g. of aluminum chloride and 21 g. of dry benzene was stirred at room temperature (about 30°) while a solution of 11 g. of ethyl-1-C^{14} chloride (0.578 μc./m. mole) in 27 g. of cold dry benzene was added dropwise. The addition required 5 min.; stirring at room temperature was continued for an additional 1.25 hr. The reaction mixture was decomposed with ice water and worked up in the usual way. Fractional distillation through a 50-cm. glass helix-packed column gave 5.6 g. of ethylbenzene, b.p. 133–136° and 1.2 g. of diethylbenzene, b.p. 172–178°.

A 1-ml. sample of the ethylbenzene fraction was oxidized with 5 g. of potassium permanganate as described above. The benzoic acid produced was recrystallized from 50% ethyl alcohol; m.p. 120–121°. Radioassay of a 5.2 mg. sample gave 0.555 μc./m. mole. The remaining benzoic acid was sublimed; radioassay of an 11.0-mg. sample gave 0.556 μc./m. mole, and of a 13.7-mg. sample, 0.555 μc./m. mole. The difference in the radioactivity of the ethyl-1-C^{14} chloride and the benzoic acid corresponded to 4.0% isomerization accompanying alkylation.

A 1-ml. sample of the diethylbenzene fraction was oxidized by the same procedure, using 11 g. of potassium permanganate. The phthalic acid produced was recrystallized from 50% ethyl alcohol; 327 mg. was obtained. A 6.2-mg. sample radioassayed gave 1.11 μc./m. mole. The phthalic acid was recrystallized; a 5.8-mg. sample radioassayed gave 1.11 μc./m. mole. The difference in the radioactivity of the ethyl-1-C^{14} chloride and the phthalic acid corresponded to 4.0% isomerization *per ethyl group* accompanying alkylation.

A second alkylation was carried out which was identical with the above except that the activity of the ethyl-1-C^{14} chloride was 0.603 μc./m. mole, and the amount of aluminum chloride used was 15.0 g. rather than 1.5 g. The amounts of ethylbenzene and diethylbenzene obtained from this reaction were 2.18 g. and 2.32 g., respectively.

Oxidation of a sample of the ethylbenzene gave benzoic acid, which was recrystallized twice from 50% ethyl alcohol and then sublimed. Radioassay of 13.2-mg. and 11.1-mg. samples gave 0.555 and 0.555 μc./m. mole, respectively, corresponding to 8.0% isomerization.

Oxidation of a sample of the diethylbenzene gave phthalic acid, which was recrystallized twice from 60% ethyl alcohol. Radioassay of 15.0-mg. and 8.3-mg. samples gave 1.11 and 1.13 μc./m. mole, respectively, the average corresponding to 7.8% isomerization *per ethyl group* accompanying alkylation.

Acknowledgment. Professor H. C. Brown suggested repeating the alkylation reaction at a lower temperature. We are indebted to him for this suggestion and for other helpful discussion.

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Acidic Properties of Tetrazole Derivatives in a Nonaqueous Medium[1]

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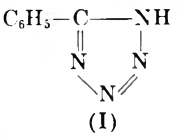
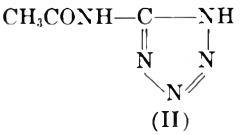
Herbst and co-workers have recently described certain tetrazole derivatives and called attention to their acidic properties.[2,3] They made the prediction[2] that 5-acetylaminotetrazole might react as a dibasic acid in nonaqueous media.

We have titrated 5-phenyltetrazole (I) and 5-



(I)



(II)

acetylaminotetrazole (II)[4] in ethylenediamine solution, using sodium aminoethoxide as the base and determining the endpoints potentiometrically with antimony electrodes.[5]

The results are given in Table I.

TABLE I

NEUTRALIZATION EQUIVALENTS

Substance	Calcd.	Found
5-Phenyltetrazole	146.2	149.9
5-Acetylaminotetrazole		
First hydrogen	127.1	130.4
Both hydrogens	63.6	64.7

Two inflections very near the calculated values in the titration curve for compound II showed that it does behave as a dibasic acid under these conditions.

As the stronger of two acids will titrate before the weaker in a mixture,[5] compound I was titrated in admixture with benzoic acid, and I and II each with 3,5-dimethylphenol in order to get a qualitative comparison of their acidic strengths. It was found that I has approximately the same strength

TABLE II

TITRATION OF MIXTURES

Mixture	Sample (G.)	Titrant: Normality	Titrant: Ml. calcd.	Titrant: Ml. found
5-Phenyltetrazole	0.0532	0.185	1.97	
Benzoic acid	0.0997		4.41	
Total			6.38	6.51
5-Phenyltetrazole	0.0671	0.185	2.48	2.70[a]
3,5-Dimethylphenol	0.1027		4.54	
Total			7.02	7.40
5-Acetylamino-tetrazole	0.1031	0.236	3.44	3.41[a]
			3.44	
3,5-Dimethylphenol	0.0516		1.79	
Total			8.67	8.61

[a] First inflection.

(1) Publication authorized by the Chief, Illinois State Geological Survey.

(2) R. M. Herbst and W. L. Garbrecht, *J. Org. Chem.*, 18, 1283 (1953).

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

(4) Samples kindly provided by Dr. R. M. Herbst, Michigan State University, East Lansing, Mich.

(5) M. L. Moss, J. H. Elliott, and R. T. Hall, *Anal. Chem.*, 20, 784 (1948).

as benzoic acid, and that the acidic strength of the second hydrogen of II is about the same as that of the phenol. These results are given in Table II.

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Potential Anticancer Agents.[1] III. 3′-Amino-3′-deoxyadenosine

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The synthesis of 3′-amino-3′-deoxyadenosine from chloromercuri-6-benzamidopurine and 2,5-di-*O*-benzoyl-3-deoxy-3-phthalimido-β-D-ribofuranosyl chloride was described by Baker, Schaub, and Kissman in 1955.[2] Since additional amounts of this biologically active nucleoside were required for pharmacological evaluation, its synthesis was repeated; the opportunity was taken to use two later modifications in nucleoside synthesis.

The first modification was the use of pure chloromercuri-6-benzamidopurine, prepared by the Fox method;[3] this procedure has previously led to higher yields of nucleosides.[4] The second modification employed was the deacylation of the blocked nucleoside with *n*-butylamine in boiling methanol.[5] By these two modifications, 3′-amino-3′-deoxyadenosine crystallized from the methanolic butylamine reaction mixture in 66% yield (based on chloro sugar) and was pure as shown by paper chromatography.

The earlier described procedure[2] required ion exchange chromatography for isolation and the over-all yield from the sugar halide was 31%. Thus, the above two new modifications in nucleoside synthesis more than doubled the previous yield.

EXPERIMENTAL[6,7]

3′-Amino-3′-deoxyadenosine. A mixture of 11.8 g. of chloromercuri-6-benzamidopurine[8] and 11.8 g. of Celite[9] suspended in 1180 ml. of xylene was distilled with stirring until no more water was removed (about 360 ml. of distillate). After a warm solution of 10.2 g. of crystalline 2,5-di-*O*-benzoyl-3-deoxy-3-phthalimido-β-D-ribofuranosyl chloride[10] in 210 ml. of xylene had been added, the mixture was heated under reflux for 3 hr. The hot solution was filtered and the filter cake was washed with 200 ml. of hot toluene. The combined filtrate and washings were concentrated to dryness *in vacuo*. The filter cake was extracted with five 100-ml. portions of boiling chloroform. The residue from the toluene-xylene concentration was dissolved in the combined chloroform extracts. The chloroform solution was washed with two 200-ml. portions of 30% aqueous potassium iodide solution, then with 200 ml. of water. The chloroform solution was dried over magnesium sulfate, then evaporated to dryness to yield 17.0 g. of cream colored solid; λ_{max}^{KBr} 2.92μ (NH, OH); 5.63μ (imido C=O); 5.81μ (benzoate and imido C=O); 7.90μ (benzoate O=C—O); 8.96μ (C—O—C).

The crude blocked nucleoside (17.0 g.) was dissolved in 210 ml. of methanol containing 30 ml. of *n*-butylamine. This solution was heated under reflux for 6 hr. After 3 hr. heating, the solution began to deposit a white, crystalline solid. The mixture was cooled at 0° overnight, then filtered. The white, crystalline precipitate was washed with methanol, then dried to yield 3.57 g. (66% based on chloro sugar) of 3′-amino-3′-deoxyadenosine, m.p. 265–267° (dec.); λ_{max}^{KBr} 3.00, 3.17μ (OH, NH); 6.00, 6.23, 6.37μ (adenine double bond structure); 9.08, 9.28, 9.64μ (C—O—). The paper chromatogram[7] contained a single spot at R_{Ad} 1.25.

Baker, Schaub, and Kissman[2] reported a m.p. 260–261° (dec.).

The methanol mother liquors contained an additional 2% of 3′-amino-3′-deoxyadenosine along with about 2% of adenine, as shown by paper chromatography.[7]

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(1) This program is under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, and is in collaboration with the Sloan-Kettering Institute for Cancer Research.

(2) B. R. Baker, R. E. Schaub, and H. M. Kissman, *J. Am. Chem. Soc.*, **77**, 5911 (1955).

(3) Footnote 21 of reference (4).

(4) B. R. Baker, K. Hewson, H. J. Thomas, and J. A. Johnson, Jr., *J. Org. Chem.*, **22**, 954 (1957).

(5) L. Goldman, J. W. Marsico, and R. B. Angier, *J. Am. Chem. Soc.*, **78**, 4173 (1956).

(6) The infrared spectra were determined with a Perkin-Elmer Model 21 spectrophotometer. The melting point was taken on a Fisher-Johns apparatus and is uncorrected.

(7) The paper chromatograms were run with 5% aqueous disodium phosphate by the descending procedure on Whatman No. 1 paper. Adenine was used as a standard and arbitrarily assigned R_{Ad} 1.00. The distance moved by the nucleoside spot was assigned an R_{Ad} value with reference to adenine. The spots were located by visual examination with an ultraviolet lamp.

(8) From 6-benzamidopurine as described for the preparation of chloromercuri-2,6-diacetamidopurine by B. R. Baker and K. Hewson, *J. Org. Chem.*, **22**, 959 (1957).

(9) An analytical grade product of Johns-Manville Corp.

(10) B. R. Baker, J. P. Joseph, and R. E. Schaub, *J. Am. Chem. Soc.*, **77**, 5905 (1955).

Preparation of Acetals and Ketals from Enol Esters

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The reaction of an alcohol and an enol ester to form acetals or ketals is catalyzed by mercuric oxide in combination with boron trifluoride (or mercuric sulfate alone).[1] This catalyst combination was observed to effect a very vigorous reaction, as has been reported. However, we have found that the reaction of ethanol and isopropenyl acetate had an induction period of 5 to 8 minutes when the ester was added to the ethanol containing the mixed catalyst at 30°.

The induction period was eliminated and the yields of ketals were improved by using mercuric

(1) W. J. Croxall, F. J. Glavis, and H. T. Neher, *J. Am. Chem. Soc.*, **70**, 2805 (1948).

acetate instead of mercuric oxide or by milling the mercuric oxide in ethanol with a mortar and pestle.[2] A comparison of the results using these mercuric catalysts for the preparation of diethyl ketal is shown in Table I.

TABLE I

COMPARISON OF MERCURIC CATALYSTS FOR THE REACTION OF ETHANOL AND ISOPROPENYL ACETATE[a]

Hg^{++} Catalyst, G.	Induction Time, Min.	Total Reaction Time, Min.	Yield, %
Red HgO, 12.5	6	24	61[b]
Red HgO (milled), 12.5	1	17	71[c]
$Hg(OAc)_2$, 18.4	<1	17	70[d]

[a] For each of these experiments, 12.5 moles of isopropenyl acetate was reacted with 37.5 moles of ethanol at 45 to 50° in the presence of 6.2 g. (contained) of BF_3 in ethyl ether. [b] This yield is the average of 8 experiments for which the yields varied from 53 to 68%. [c] This yield is the average of 3 experiments for which the yields varied from 67 to 74%. [d] This yield is the average of 8 experiments for which the yields varied from 68 to 73%.

Although these experiments were conducted with a 3 to 1 molar ratio of ethanol to isopropenyl acetate, in general, a 2.2 to 1 mole ratio provides yields which are nearly as good. Excess amounts of water-soluble alcohols in the reaction mixture preferably are extracted by water after neutralizing the co-product acetic acid. If this is not done sufficient water is retained in the mixture to effect partial hydrolysis of the ketal during distillation.

A comparison of our results to those reported in the literature[1] is given in Table II. For the preparation of dibutyl acetal, our results are the same as the reported yields but for the preparation of ketals we obtained better yields.

The results obtained in this study suggest, in agreement with those of Watanabe and Conlon,[3] that the effective form of mercury acting as a catalyst for general exchange reactions of vinyloxy compounds is mercuric acetate (or mercuric salts of organic acids) rather than mercuric oxide,[1] mercuric phosphate,[1] or mercuric sulfate.[4] The addition of mercuric acetate in the presence of alcohols to carbon-carbon double bonds proceeds according to Markownikoff's rule.[5] Addition compounds of this type and their derivatives have been isolated in many instances.[6-8] This reaction also has been adapted to the quantitative determination of carbon-carbon double bonds.[9]

Intermediates similar to those proposed by Watanabe and Conlon can be written in conjunction with acid-catalyzed steps to explain the conversion of vinyl ester to vinyl ether to acetal. We believe, however, that these steps can be simplified somewhat as follows:[10]

$$Hg(OAc)_2 \rightleftharpoons HgOAc^+ + OAc^- \quad (1a)$$

$$HgOAc^+ + AcOCH{=}CH_2 + ROH \rightleftharpoons \begin{matrix}AcO\\RO\end{matrix}\!\!>\!CHCH_2HgOAc + H^+ \quad (1b)$$

$$\begin{matrix}AcO\\RO\end{matrix}\!\!>\!CHCH_2HgOAc + ROH \xrightarrow{\text{acid}} \begin{matrix}RO\\RO\end{matrix}\!\!>\!CHCH_2HgOAc + HOAc \quad (1c)$$

$$\begin{matrix}RO\\RO\end{matrix}\!\!>\!CHCH_2HgOAc + AcOCH{=}CH_2 \rightleftharpoons \begin{matrix}AcO\\RO\end{matrix}\!\!>\!CHCH_2HgOAc + ROCH{=}CH_2 \quad (1d)$$

$$ROCH{=}CH_2 + ROH \xrightarrow{\text{acid}} \begin{matrix}RO\\RO\end{matrix}\!\!>\!CHCH_3 \quad (1e)$$

Equations 1a and 1b are essentially the same as those which have been given for the start of vinyl transetherification or transesterification.[3] Step 1c must be acid-catalyzed to permit the over-all reaction to proceed.[11] Equation 1d for the formation

(2) The water solubility of red HgO can be increased by grinding. See F. Ephraim, *Inorganic Chemistry*, 6th Ed., Interscience Publishers, Inc., N. Y., 1954, p. 490.

(3) W. H. Watanabe and L. E. Conlon, *J. Am. Chem. Soc.*, **79**, 2828 (1957).

(4) R. L. Adelman, *J. Am. Chem. Soc.*, **75**, 2678 (1953); D. D. Coffman, G. H. Kalb, and A. B. Ness, *J. Org. Chem.*, **13**, 223 (1948).

(5) F. C. Whitmore, *Organic Compounds of Mercury*, New York Chemical Catalogue Company, N. Y., 1921, p. 31.

(6) R. Adams, F. L. Roman, and W. N. Sperry, *J. Am. Chem. Soc.*, **44**, 1781 (1922).

(7) G. Wright, *J. Am. Chem. Soc.*, **57**, 1993 (1935).

(8) I. F. Lutsenko, R. M. Khomutov, and L. V. Eliseeva, *Bull. acad. sci. U.S.S.R. Div. Chem. Sci. S.S.R.* (English translation), **No. 2**, 173 (1956).

(9) R. W. Martin, *Anal. Chem.*, **21**, 921, 1194 (1949).

(10) For vinyl transetherification (or transesterification) a "symmetrical intermediate" would not seem to be an essential requirement.[3] The following equation would lead to the same result:

$$R'OH + ROCH{=}CH_2 + HgOAc^+ \rightleftharpoons \begin{matrix}R'O\\RO\end{matrix}\!\!>\!CHCH_2HgOAc + H^+ \rightleftharpoons ROH + R'OCH{=}CH_2 + HgOAc^+$$

The over-all conversion obtained would depend upon the mole ratios of reactants, the relative reactivities of the alcohols and vinyl ethers, and whether or not one of the products is removed, as for example, by distillation.

(11) One of the referees has suggested that BF_3 creates more of the reactive species, $HgOAc^+$ by:

$$Hg(OAc)_2 + BF_3 \rightleftharpoons HgOAc^+ + BF_3{\cdot}OAc^-$$

which is the initiating step of the reaction sequence.

TABLE II

PREPARATION OF ACETALS AND KETALS

Enol Acetate, Moles	Alcohol, Moles	Temperature[a]	Product	Observed Yield, %	Literature[1] Yield, %
Vinyl, 2.0	Butyl, 4.2	26–54°	Dibutyl acetal	88	88
Isopropenyl, 14.0	Methyl, 29.4	29–54°	Dimethyl ketal	53[b]	—
Isopropenyl, 12.5	Ethyl, 37.4	30–50°	Diethyl ketal	70[c]	55
Isopropenyl, 10.0	Butyl, 22.0	10–55°	Dibutyl ketal	83[d]	63
Isopropenyl, 6.0	Allyl, 12.6	20–25°	Diallyl ketal	50[e]	32

[a] These values represent the temperature ranges from the start of ester addition until the temperatures were moderated by cooling. The temperatures were then controlled at 50 ± 5° by cooling. For the preparation of diallyl ketal no cooling was required. [b] For this experiment, 3.6 g. BF_3 and 10.0 g. $Hg(OAc)_2$ were used. The ester addition time was 13 mins. and the total reaction time was 23 mins. The yield is the average of three expts. for which the values varied from 51 to 55%. [c] For this experiment, 7.2 g. BF_3 and 18.4 g. $Hg(OAc)_2$ were used. The ester addition time was 16 min. and the total reaction time was 18 min. The yield is the average of eight experiments for which the values varied from 68 to 73%. [d] For this experiment, 4.0 g. BF_3 and 12.0 g. $Hg(OAc)_2$ were used. The ester addition time was 10 min. and the total reaction time was 20 min. The yield is the average of two experiments for which the values were 80 and 86%. [e] For this experiment, 4.0 g. BF_3 and 12.0 g. $Hg(OAc)_2$ were used. The ester addition time was 45 min. and the total reaction time was 170 min.

of vinyl ether is a necessary consequence of Adelman's[4] demonstration that vinyl ethers are intermediates in the conversion of vinyl esters to acetals or ketals. Finally, equation 1e is for the well-established, acid-catalyzed reaction of a vinyl ether and an alcohol to form acetals.[12]

At temperatures in excess of 25°, the reaction represented by step 1e proceeds fairly rapidly. At 40° this reaction is extremely rapid so that at these temperatures one would not expect to isolate the vinyl ether intermediate. We have found that at −25° the rate of the acid-catalyzed addition of an alcohol to a vinyl ether is very slow (see Experimental section) and hence under Adelman's conditions for vinyl ester exchange with an alcohol,[4] the vinyl ether has a sufficiently long existence to permit its isolation in good yields. The effective catalyst system under Adelman's conditions is probably mercuric acetate and sulfuric acid, not mercuric sulfate. These two reagents were added to the reaction mixtures, presumably to form mercuric sulfate. Even if mercuric sulfate were added, one should expect sufficient exchange with the by-product acetic acid to provide some mercuric acetate.

EXPERIMENTAL

Diethyl ketal. To a mixture of 1725 g. (37.5 moles) of ethanol, 18.4 g. of mercuric acetate, and 28 ml. of 26% boron trifluoride in diethyl ether at 30°, there was added 1250 g. (12.5 moles) of isopropenyl acetate over a period of 15 min. while maintaining the mixture at 45 to 50° by external cooling. Two minutes after all of the isopropenyl acetate was added, the mixture was poured into 2200 g. of 25% sodium hydroxide with stirring and cooling. The water layer was removed and the organic layer washed first with 400 ml. of 0.01*N* sodium hydroxide followed by 3 washings with 200 ml. of 0.01*N* sodium hydroxide. Rapid distillation of the organic layer provided 1145 g. (69% yield) of diethyl ketal which boiled at 110–113°.

Dibutyl ketal. A mixture of 1635 g. (22 moles) of butanol, 12.5 ml. of 32% boron trifluoride in diethyl ether, and 12 g. of mercuric acetate was cooled to 5° and 1010 g. (10.1 moles) of isopropenyl acetate was added over a period of 10 min. The temperature of the reaction mixture was maintained at 45 to 55° during the addition by means of an ice water bath. The mixture was cooled to 18° over a 10-min. period and then 1500 g. of 30% aqueous sodium hydroxide was added over a 3-min. period (max. temp. of 53°). The upper layer (1924 g.) was distilled to provide 1521 g. (80% yield) of dibutyl ketal which boiled at 74°/10 mm. Hg.

Addition of butanol to vinyl butyl ether. A. Reaction at 40°. To 111 g. (1.5 moles) of butanol there was added 0.21 g. of concentrated sulfuric acid and the mixture was warmed to 40°. One mole (100 g.) of vinyl butyl ether was added as rapidly as possible (3 min.) and the temperature maintained between 39 and 41° by cooling. As soon as all of the ether was added, a sample was removed and analyzed immediately for vinyl butyl ether.[13] More than 95% of the vinyl butyl ether had reacted during this time.

B. Reaction at −25°. A mixture of 50 g. (0.5 mole) of vinyl butyl ether and 54 g. (0.73 mole) of butanol was added to a 2- by 4-in. wide-mouth tube which narrowed to a 1- by 6-in. round bottom tube. The tube and contents were immersed in a Dewar flask and the temperature was adjusted to −25° by means of Dry Ice and acetone. The mixture was analyzed for vinyl butyl ether, then acidified with 0.1 g. of sulfuric acid in 1 ml. of butanol. During the entire experiment the temperature was maintained at −25° ± 4°. The conversions of vinyl butyl ether to dibutyl acetal after 1 hr., 4 hr., and 6.5 hr. were 4.9%, 12.5%, and 16.8%, respectively. The mixture was then allowed to warm slowly to room temperature. When the temperature reached 30°, the reaction was proceeding at a sufficiently rapid rate for the temperature to rise to 40° in 3 min. The mixture was cooled to room temperature and analyzed for vinyl butyl ether. More than 98% of the vinyl butyl ether was converted to the acetal.

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(12) H. S. Hill, *J. Am. Chem. Soc.*, **50**, 2725 (1928); W. Reppe and K. Baur, U. S. Patent **2,000,252** (May 7, 1935).

(13) The analysis for vinyl butyl ether involved a method which has not been published and uses a mercuric acetate reagent which is a modification of that reported by Martin.[9]

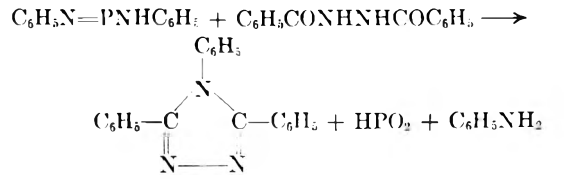
Preparation of Triaryl-*s*-triazoles from Diaroylhydrazines[1]

ERWIN KLINGSBERG

Received February 6, 1958

Although the formation of 3,4,5-triaryl-*s*-triazoles from diaroylhydrazines and primary amines is a well-known "textbook" reaction, it has been little used and its preparative value is dubious. Busch,[2] for example, recommends phosphorus pentoxide as a catalyst, but in our hands this gave only a 20–30% yield of partially purified triphenyltriazole. Bhagat and Rây[3] prepared several triaryltriazoles by fusing dibenzoylhydrazine with the amine in the presence of zinc chloride, but they give no yield data, and the reaction does not seem to have been investigated since.

In the search for a good way to carry out this reaction, it seemed that phenylphosphazoanilide might be suitable. Grimmel, Guenther, and Morgan[4]



have reported that this substance, which is readily prepared from phosphorus trichloride and aniline, converts acids to their anilides:

$$C_6H_5NH_2 + PCl_3 \longrightarrow C_6H_5N{=}PNHC_6H_5 +$$
$$2RCOOH \longrightarrow 2RCONHC_6H_5 + HPO_2$$

A reaction with dibenzoylhydrazine can be formulated as follows:

It was in fact found that phenylphosphazoanilide can be prepared in *o*-dichlorobenzene and used *in situ* at reflux to convert *N*,*N'*-dibenzoylhydrazine to a good yield of the desired triazole.

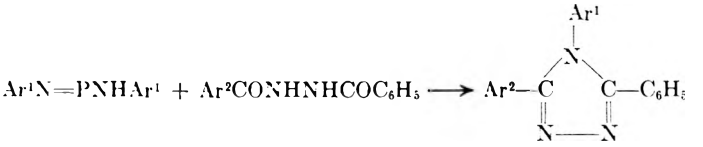
The scope of the reaction was then explored in a series of experiments, and it appears to be fairly general within certain limits.

All experiments were carried out on a 0.010 mole scale by the general procedure described below. No experiment was repeated. It will be seen that 85–95% yields of product were obtained from dibenzoylhydrazine and the phosphazo derivatives of aniline, *p*-toluidine, *m*-toluidine, and *p*-chloroaniline. *o*-Toluidine and 2-naphthylamine gave distinctly inferior results, although there was no difficulty in obtaining the triazole. *N*-Benzoyl-*N'*-isonicotinoylhydrazine and aniline gave excellent results.

A limitation on the reaction is its apparent inapplicability to triazoles with aliphatic substituents. Thus no product was obtained from *N*-acetyl-*N'*-benzoylhydrazine and aniline, while dibenzoylhydrazine and cyclohexylamine gave diphenyloxadiazole.

TABLE I

ARYLPHOSPHAZOARYLIDE TRIAZOLE SYNTHESIS



Ar^1=	Ar^2=	Crude Product M.P.	Crude Product Yield	Pure Product M.P.	Literature M.P.
C_6H_5	C_6H_5	299.5°–300.5°	95%	299–300°[a]	292°[2,5]
p-MeC_6H_4	C_6H_5	301–2°	88%	301–302°[b]	296–7°[3]
o-MeC_6H_4	C_6H_5	159–179°	72%	191–192°[c]	184°[3]
m-MeC_6H_4	C_6H_5	254.5°–255.5°	83%	256–257°	250°[3]
p-ClC_6H_4	C_6H_5	260.5°–262°	88%	261.5–262°	New cpd.[d]
C_6H_5	4-pyridyl	262–8°	95%	268–269°[e]	New cpd.[f]
2-$C_{10}H_7$	C_6H_5	252–6°	52%	275.5–276.5°[g]	New cpd.[h]

[a] *Anal.* Calcd. for $C_{20}H_{15}N_3$: C, 80.9; H, 5.1; N, 14.1. Found: C, 80.8; H, 5.2; N, 14.4. [b] *Anal.* Calcd. for $C_{21}H_{17}N_3$: C, 81.1; H, 5.5; N, 13.5. Found: C, 81.0; H, 5.5; N, 13.3. [c] Crystallized from dil. acetic acid followed by methylcyclohexane. [d] *Anal.* Calcd. for $C_{20}H_{14}N_3Cl$: C, 72.3; H, 4.2; N, 12.7; Cl, 10.7. Found: C, 72.3; H, 4.0; N, 12.5; Cl, 10.3. [e] Crystallized from xylene. [f] *Anal.* Calcd. for $C_{19}H_{14}N_4$: C, 76.5; H, 4.7; N, 18.8. Found: C, 76.6; H, 5.0; N, 18.7. [g] Crystallized from dil. acetic acid followed by xylene. [h] *Anal.* Calcd. for $C_{24}H_{17}N_3$: C, 83.0; H, 4.9; N, 12.1. Found: C, 83.1; H, 4.6; N, 12.0. [i] *N*-benzoyl-*N'*-isonicotinoylhydrazine, m.p. 226.5–228.5°, prepared according to U.S. Patent 2,689,852.

EXPERIMENTAL

General procedure. To a solution or suspension of 0.060 mole of the amine in 20–30 ml. of *o*-dichlorobenzene was slowly added, with shaking, 0.96 ml. (1.51 g.; 0.011 mole) of

(1) Presented at the ACS Meeting-in-Miniature of the North Jersey Section at Seton Hall University on January 27, 1958.

(2) M. Busch, *J. Prakt. Chem.*, **89**, 552 (1914).

(3) K. L. Bhagat and J. N. Rây, *J. Chem. Soc.*, 2357 (1930).

(4) H. W. Grimmel, A. Guenther, and J. F. Morgan, *J. Am. Chem. Soc.*, **68**, 539 (1946).

(5) R. Stollé, *J. Prakt. Chem.*, **73**, 288 (1906).

phosphorus trichloride. Reaction was immediate, and could be completed by gentle warming on the steam bath for a few moments.

After the addition of 0.010 mole of the diaroylhydrazine, the mixture was stirred and refluxed for 3 hr. in an oil bath at 190–200°. Efficient stirring is desirable. In an occasional experiment, trace amounts of byproducts were found to undergo spontaneous ignition in the condenser. This does no harm on the 0.010 mole scale, but can be prevented by operating in a nitrogen atmosphere. After cooling, the product was collected and digested in hot water or dilute hydrochloric acid. It was purified by crystallization from glacial or dilute acetic acid.

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1-Phenylpropyne

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Received March 24, 1958

1-Phenylpropyne, $C_6H_5C{\equiv}CCH_3$, has been synthesized in a number of ways including (*a*) methylation of phenylacetylene with methyl iodide,[1] methyl sulfate,[2] or methyl toluenesulfonate,[3] (*b*) dehydrobromination of 2-bromo-1(or -3)-phenylpropene by fused[4] or alcoholic[5] potassium hydroxide, or by magnesium[6] in ether, and (c) an approach[7] from benzaldehyde and methyl ethyl ketone involving steps of condensation, oxidation, bromination, and dehydrobromination.

It seemed to us that dehydrochlorination of 2-chloro-1(or -3)-phenylpropene offered possibilities of a better synthesis. Zaki and Iskander[8] prepared this equilibrium mixture of chlorides by treating phenylacetone with phosphorus pentachloride in hot benzene solution, then distilling the product and washing it with ice water.

We found that benzene (solvent) could be omitted with no loss of yield. The reactants (110 g. of phenylacetone and 208 g. of phosphorus pentachloride) were mixed directly and heated for an hour at 100°. Then the phosphoryl chloride was distilled off under diminished pressure and the two desired chlorides in the residue were collected by distillation 105–125° (25 mm.); the yield was 110 g. (88%), which is the same as that reported by Zaki and Iskander.

The 110 g. of product was refluxed for 3 hr. with 55 g. of sodium hydroxide pellets in 120 ml. of absolute ethyl alcohol. Decomposition with water, extraction with benzene, drying, and distillation yielded 70 g. of 1-phenylpropyne boiling at 90° and 20 mm. This represents an 84% yield based on the last step, or a 74% yield based on the phenylacetone.

In another similar run, 164 g. of 1-phenylpropyne (88% yield) was obtained from 245 g. of the mixture of 2-chloro-1-phenylpropene and 2-chloro-3-phenylpropene.

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(1) J. U. Nef, *Ann.*, **310**, 333 (1900).
(2) M. Bourguel, *Compt. rend.*, **186**, 1212 (1928).
(3) R. Truchet, *Ann. chim.*, [10] **16**, 309 (1931).
(4) M. Tiffeneau, *Compt. rend.*, **135**, 1347 (1902); *Ann. chim.*, [8] **10**, 169 (1907).
(5) R. Lespieau and Garreau, *Compt. rend.*, **171**, 112 (1920); R. Lespieau, *Bull. soc. chim.*, [4] **29**, 533 (1921); M. Bourguel, *Ann. chim.*, [10] **3**, 350 (1925).
(6) C. D. Hurd and C. N. Webb, *J. Am. Chem. Soc.*, **49**, 557 (1927).
(7) M. T. Bogert and D. Davidson, *J. Am. Chem. Soc.*, **54**, 334 (1932).
(8) A. Zaki and Y. Iskander, *J. Chem. Soc.*, 68 (1943).

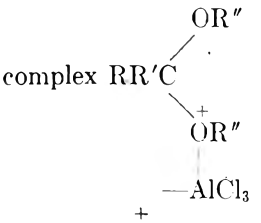
Communications TO THE EDITOR

Reduction of Acetals to Ethers by Means of Lithium Aluminum Hydride–Aluminum Chloride

Sir:

Acetals and ketals are not reduced by lithium aluminum hydride.[1] However, Doukas and Fontaine have described the reduction of a spirostanol (ketal) to a furostanol (ether) by means of ethereal lithium aluminum hydride containing hydrogen chloride or hydrogen bromide (but not other acids).[2] It appeared to us that the reagent in this reduction might be lithium aluminum hydride–aluminum chloride (or bromide).[3] Evidence for this view has now been obtained by the reduction of benzaldehyde diethyl acetal to benzyl ethyl ether (72% yield, b.p. 75–77°/23 mm., n_D^{20} 1.4889; lit.[4] b.p. 70–71.5°/12 mm., n_D^{20} 1.4954), of acetophenone diethyl ketal to α-phenethyl ethyl ether (59% yield, b.p. 88–90°/36 mm., n_D^{25} 1.4849; lit.[5] b.p. 89°/31 mm., n_D^{25} 1.4846), of butyraldehyde diethyl acetal to *n*-butyl ethyl ether (*ca.* 47% yield, b.p. 90–92°/745 mm., n_D^{25} 1.3790; lit.[6] b.p. 92.3°/760 mm., n_D^{25} 1.3798—part of this material was recovered as an azeotrope with ethanol) and of cyclohexanone diethyl ketal to cyclohexyl ethyl ether (61% yield, b.p. 147–149°/750 mm., n_D^{20} 1.4351; lit.[7] b.p. 148.5–149.5°/763 mm., n_D^{20} 1.43505) by means of the lithium aluminum hydride–aluminum chloride (1:4 ratio) reagent. The four ether products were identical in infrared spectra with authentic samples.

The reduction of acetals and ketals, $RR'C(OR'')_2$ to ethers $RR'CHOR''$ by means of $LiAlH_4$–$AlCl_3$ may involve chloroethers $RR'CClOR''$ as intermediates, in as much as such α-chloroethers are known to be reduced readily to ethers.[1] Alternatively, it may involve hydride displacement on the



complex $RR'C(OR'')(OR'')^+AlCl_3$, possibly *via* the resonating cation $RR'C^+-OR'' \longleftrightarrow RR'C=\overset{+}{O}R''$. An analogy is available in the reduction of α-aminoethers to amines by means of $LiAlH_4$ alone.[1] We are undertaking further work to elucidate the course of the acetal reduction and to extend its scope.

After this work was completed, a report appeared describing the hydrogenolysis of *p*-methoxybenzyl ethers, $p\text{-}CH_3OC_6H_4CH_2OR$ to the corresponding toluenes, $p\text{-}CH_3OC_6H_4CH_3$ by means of $LiAlH_4$–$AlCl_3$.[8] It might be noted that these ethers are vinylogs of acetals, and that their reduction by the mixed reagent is related to the reduction of *p*-aminobenzyl alcohols to *p*-aminotoluenes by $LiAlH_4$ alone in similar fashion as the reduction of acetals is related to that of α-aminoethers.

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(1) N. G. Gaylord, "Reduction with Complex Metal Hydrides," Interscience Publishers, Inc., New York, N. Y., 1956.

(2) H. M. Doukas and T. D. Fontaine, *J. Am. Chem. Soc.*, **75**, 5355 (1953).

(3) *cf.* E. Wiberg and M. Schmidt, *Z. Naturforschg.*, **6b**, 333, 460 (1951); E. Wiberg and A. Jahn, *Z. Naturforschg.*, **7b**, 580, 581 (1952); R. F. Nystrom, *J. Am. Chem. Soc.*, **77**, 2544 (1955); A. J. Birch and M. Slaytor, *Chem. & Ind. (London)*, 1524 (1956); G. LeNy and Z. Welvart, *Compt. rend.*, **245**, 434 (1957); O. H. Wheeler and J. L. Mateos, *Chem. & Ind. (London)*, 395 (1957); B. R. Brown, *J. Chem. Soc.*, 2756 (1952); J. Broome and B. R. Brown, *Chem. & Ind. (London)*, 1307 (1956); B. R. Brown and A. M. S. White, *J. Chem. Soc.*, 3755 (1957); E. L. Eliel and D. Delmonte, *J. Am. Chem. Soc.*, **78**, 3226 (1956), **80**, 1744 (1958); J. L. Bailey, *Biochem. J.*, **60**, 170 (1955); R. A. Berger and R. F. Nystrom, *Abstracts, Miami, Fla. Meeting, Am. Chem. Soc.*, 51-O (1957).

(4) C. R. Hauser and S. W. Kantor, *J. Am. Chem. Soc.*, **73**, 1437 (1951); F. Drahowzal and D. Klamann, *Monatsh.*, **82**, 594 (1951).

(5) K. Mislow, *J. Am. Chem. Soc.*, **73**, 4943 (1951).

(6) J. F. Morris and G. W. Rigby, *J. Am. Chem. Soc.*, **54**, 2098 (1932).

(7) A. I. Vogel, *J. Chem. Soc.*, 1809 (1948).

(8) B. R. Brown and C. A. Somerfield, *Proc. Chem. Soc.*, 7 (1958).