β-Chloroethyl Carbonates and S-β-Chloroethyl Thiolcarbonates (Tables II and III).—Ethylene sulfide (1 mole) was slowly added to 1 mole of alkyl chloroformate or alkyl chlorothiolformate containing a few drops of pyridine while maintaining the reaction mixture at 10–20°. After the addition was completed, the temperature was slowly raised to 80° and the solution was stirred for 2 hr. The crude products were vacuum distilled. The infrared spectra showed carbonyl absorption between 1640 cm.$^{-1}$ and 1670 cm.$^{-1}$ (—S—CO—S—)[21] and between 1720 cm.$^{-1}$ and 1740 cm.$^{-1}$ (—O—CO—S—).[21] The yields, analysis, boiling points, and the indices of refraction of these compounds are given in Tables II and III.

S-Ethyl N-β-Chloroethyl-N-methyl Thiolcarbamate (Table IV).—A solution of 50 g. (0.875 mole) of N-methylaziridine in 150 ml. of ether was added to a solution of 111.5 g. (0.875 mole) of ethyl chlorothiolformate in 250 ml. of ether at a rate sufficient to maintain moderate refluxing. After the addition was complete, the turbid solution was refluxed for 2 hr. The reaction mixture was filtered and washed with dilute sulfuric acid and water. The ether was removed and the residue vacuum distilled. The same procedure was used to prepare β-chloroethyl N-β-chloroethyl-N-methylcarbamate. The yield, physical properties, and analysis of these compounds (15) and (16), respectively, appear in Table IV.

S-, O-, and N-Vinyl Carbonic Acid Derivatives.—The β-chloroethyl compounds (0.5 mole) were dissolved in 100 ml. of absolute *t*-butyl alcohol and added dropwise to a freshly prepared solution of 0.5 mole of potassium *t*-butoxide in 300–400 ml. of absolute *t*-butyl alcohol. The temperature was kept at 50–70° during the reaction. After the addition was completed, the slurry was stirred for at least 1–2 hr., usually until the reaction mixture was neutral or only weakly basic. The reaction mixture was cooled, neutralized with glacial acetic acid, and 100 ml. of ether were added to complete the precipitation of the salt. The slurry was filtered, the solvent evaporated, and the residue vacuum distilled. The analysis, yields, and physical properties of the monomers are reported in Tables V, VI, and VII.

Polyethylene sulfide[15] and/or 1,4-dithiane[16] were isolated as side products in dehydrohalogenation reactions. Both compounds were identified by analysis, infrared spectrum, and melting point. 1,4-Dithiane, m.p. 112–113 (m.p. 113), usually complicated the vacuum distillation by its tendency to sublime.

Anal. Calcd. for polyethylene sulfide $(C_2H_4S)_n$; C, 40.01; H, 6.61; S, 53.38. Found: C, 39.98; H, 6.80; S, 53.37.

Polymerization of the Monomers.—The monomers were polymerized in bulk with 0.3 wt. % of 2,2′-azobisisobutyronitrile as initiator in glass tubes sealed under nitrogen. The polymers were isolated by precipitation from pentane or methanol and purified by reprecipitation from tetrahydrofuran and pentane. The polymerization conditions, the viscosities, the softening points, and the solubilities of the polymer are given in Tables VIII and IX.

Hydrolysis of Poly(S-vinyl Thiolcarbamates) and Poly(S-vinyl Thiolcarbonates).—The polymers were hydrolyzed by heating under reflux in an atmosphere of prepurified nitrogen with 10% sodium hydroxide in water–alcohol until a clear solution was obtained.[18] For the case of poly(S-vinyl S-isopropyl dithiolcarbonates) the hydrolysis was completed after 5 hr. The polyvinylmercaptan was precipitated with 2 *N* hydrochloric acid, filtered, washed with water, and dried. After isolation, the polymer was insoluble in base due to oxidative cross-linking. The infrared spectrum of the polymer did not show any carbonyl absorption. Contrary to this poly(S-vinyl N,N-diethyl thiolcarbonate) did not go into solution before 20 hr. of refluxing. The infrared spectrum of the precipitated polyvinyl mercaptan still showed a weak carbonyl absorption at 1655 cm.$^{-1}$.

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Dihydroisocoumarins. IV. Reaction with N-Bromosuccinimide. A New Route to Some Isocoumarin Syntheses

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Starting from appropriate homophthalates, 6,7-dimethoxy-, 5-methoxy-7-methyl-, 5,6-dimethoxy-, and 6,7-methylenedioxyisochroman were synthesized and oxidized to the corresponding dihydroisocoumarins. These were converted into the isocoumarins with the aid of *N*-bromosuccinimide.

Previous studies[1–3] from this laboratory on the syntheses of dihydroisocoumarins involve the formation of the hetero ring from appropriate *o*-aminophenethyl alcohols; the amino group is transformed into carboxyl which lactonizes with the *o*-hydroxyethyl group to form the dihydroisocoumarins. This route, however, depends on the availability of such starting materials as *o*-nitrophenylacetates and *o*-nitrophenethyl alcohols, very few of which are readily accessible. Therefore, the alternative method based on the oxidation[4] of isochromans with selenium dioxide was adopted for the preparation of the dihydroisocoumarins. The oxidation with selenium dioxide, though proceeding normally in one case, gave dark gummy products in the other instances which required extensive purification for the isolation of the dihydroisocoumarins and consequently the yields were lowered. Subsequently, chromium trioxide proved to be a superior reagent for oxidation as the products were purer and the yields were higher.

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(1) P. K. Banerjee and D. N. Chaudhury, *J. Org. Chem.*, **26**, 4344 (1961).

(2) J. N. Srivastava and D. N. Chaudhury, *J. Indian. Chem. Soc.*, **38**, 998 (1961).

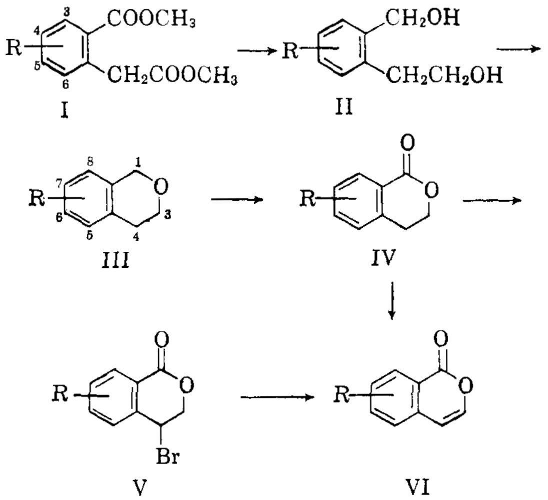
(3) P. K. Banerjee and D. N. Chaudhury, *ibid.*, **39**, 243 (1962).

(4) P. Maitte, *Ann. Chim.*, (xii), **9**, 473 (1954).

The isochromans required for the purpose were prepared from the homophthalates as the starting materials. Warnell and Shriner[5] obtained isochroman in nearly quantitative yield by vacuum distillation of homophthalyl alcohol with traces of concentrated sulfuric acid. Since substituted homophthalates are accessible, the corresponding homophthalyl alcohols were readily prepared by reduction with lithium aluminum hydride. The use of concentrated sulfuric acid for cyclodehydration of substituted homophthalyl alcohols into isochromans was precluded as it led to extensive decomposition. Phosphorus pentoxide in benzene was used initially with success only in one instance, but the reagent gave intractable products with other cases. Siegel and Coburn[6] used fused potassium acid sulfate for dehydration of homophthalyl alcohol to isochroman in rather low yield. Application of their procedure with some modification, however, proved to be a good method for the preparation of the isochromans in general.

Finally, the dihydroisocoumarins were transformed into isocoumarins with the aid of N-bromosuccinimide. In two out of the four cases, N-bromosuccinimide in the presence of benzoyl peroxide dehydrogenated the dihydroisocoumarins directly into isocoumarins whereas, in the other two instances, 4-bromodihydroisocoumarins were obtained. Such formulation of the bromo compounds is logical, since the only vulnerable point of attack under the condition is the 4-position of the δ-lactone ring. Moreover, it finds a close analogy with the work of Blair and his associates,[7] who have shown that the phthalide, meconin, is exclusively brominated with N-bromosuccinimide at the 3-position of the γ-lactone ring in spite of the available activated 4-position in the benzene nucleus. The 4-bromodihydroisocoumarins were smoothly dehydrobrominated with triethylamine to the isocoumarins and thus lends further support to the structural assignment of the intermediate bromo compounds.

Kamal, *et al.*,[8] attempted to develop a general method for the synthesis of isocoumarins from homophthalates as the starting material. Condensation with methyl formate followed by Dieckmann–Meiser cyclization of the resulting hydroxymethylene compounds furnished the intermediates, 4-carbomethoxyisocoumarins; elimination of the ester group by hydrolysis and decarboxylation gave the isocoumarins in some instances, but such elimination could not be effected in a number of cases. However, using the same starting materials, the homophthalates, our route to isocoumarin synthesis, *via* the intermediate dihydroisocoumarins, holds promise for a general method for the preparation of isocoumarins. The reaction sequence is as in I → VI. An important feature of this route is easy preparations and good yields at almost all stages.



Ia, IIa. R = 4,5-di-OCH$_3$
Ib, IIb. R = 4-CH$_3$-6-OCH$_3$
Ic, IIc. R = 5,6-di-OCH$_3$
Id, IId. R = 4,5-O$_2$CH$_2$
IIIa, IVa, VIa. R = 6,7-di-OCH$_3$
IIIb, IVb, VIb. R = 5-OCH$_3$-7-CH$_3$
IIIc, IVc, Vc, VIc. R = 5,6-di-OCH$_3$
IIId, IVd, Vd, VId. R = 6,7-O$_2$CH$_2$

The homophthalates, (Ia),[8] (Ib),[9] (Ic), and (Id) were reduced to homophthalyl alcohols, (IIa), (IIb), (IIc), and (IId), with lithium aluminum hydride, respectively. IIa with phosphorus pentoxide in boiling benzene gave the isochroman (IIIa), which was also alternatively obtained by chloromethylation of 3,4-dimethoxyphenethyl alcohol. The other isochromans, (IIIb), (IIIc), and (IIId) were obtained by vacuum distillation with fused potassium acid sulfate of the corresponding homophthalyl alcohols, (IIb), (IIc), and (IId). IIIa and IIIb were oxidized with selenium dioxide in boiling xylene to the respective dihydroisocoumarins, (IVa)[2] and (IVb) whereas chromium trioxide oxidation of IIIc and IIId furnished the dihydroisocoumarins (IVc) and (IVd), respectively. IVa and IVb, on interaction with N-bromosuccinimide in the presence of benzoyl peroxide, were dehydrogenated and gave the previously reported isocoumarins (VIa)[8] and (VIb),[8] respectively, but IVc and IVd under the same condition afforded the corresponding 4-bromodihydroisocoumarins (Vc) and (Vd); the latter were smoothly dehydrobrominated with triethylamine to the isocoumarins (VIc) and (VId), respectively.

The synthesis of other isocoumarins by this route is in progress in this laboratory.

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[5] J. L. Warnell and R. L. Shriner, *J. Am. Chem. Soc.*, **79**, 3165 (1957).

[6] S. Siegel and S. Coburn, *ibid.*, **73**, 5494 (1951).

[7] J. Blair, W. R. Logan, and G. T. Newbold, *J. Chem. Soc.*, 2443 (1956).

[8] A. Kamal, A. Robertson, and E. Tittensor, *ibid.*, 3375 (1950).

[9] E. Berner, *ibid.*, 1052 (1946).

Experimental[10]

2-Hydroxymethyl-4,5-dimethoxyphenethyl Alcohol (IIa).—To a stirred slurry of lithium aluminum hydride (1.5 g.) in dry ether (100 ml.) was added, at such a rate as to maintain reflux, a solution of methyl 2-carbomethoxy-4,5-dimethoxyphenylacetate[8] (4 g.) in dry ether (50 ml.). After refluxing for 2 hr., water was added cautiously with stirring, followed by 2 *N* sulfuric acid to produce a clear solution. It was extracted with ethyl acetate (5 × 50 ml.), the extract dried over anhydrous sodium sulfate, and the solvent removed. The residue was recrystallized from ethyl acetate–petroleum ether to give IIa as plates (2.2 g.; 70%), m.p. 113–114°.

Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62.3; H, 7.5. Found: C, 62.6; H, 7.7.

6,7-Dimethoxyisochroman (IIIa).—Phosphorus pentoxide (5 g.) was added in portions to a solution of IIa (1.5 g.) in boiling anhydrous benzene and the mixture refluxed for 45 min. The benzene solution was decanted, combined with several benzene extracts of the pasty residue, washed with 2 *N* sodium carbonate, and then water, dried over fused calcium chloride. Evaporation of the solvent left a yellow solid which on vacuum sublimation at 100–105°/1 mm. afforded IIIa as white prismatic needles (1 g.; 74%), m.p. 82–83°.

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.0; H, 7.2. Found: C, 67.7; H, 6.9.

Alternatively, IIIa was prepared by chloromethylation of 3,4-dimethoxyphenethyl alcohol.[11] To a solution of the alcohol (3 g.), formalin (3 ml.; 37%), and concentrated hydrochloric acid (1.5 ml.) in dioxane, dry hydrogen chloride was bubbled at such a rate as to ensure a temperature of 55–60°, for 0.5 hr. without external heating. The cooled reaction mixture was poured into ice–water, extracted with ether (3 × 20 ml.), the extract washed with water, dried over anhydrous sodium sulfate, and evaporated. The residue was sublimed under vacuum at 100–105°/mm. to give the isochroman (IIIa) as tiny prismatic needles (1.6 g.; 50%), m.p. 80–82°, undepressed on admixture with the authentic specimen prepared by the other route above.

3,4-Dihydro-6,7-dimethoxyisocoumarin (IVa).—A solution of IIIa (1.6 g.) in xylene (20 ml.) was treated with selenium dioxide (1.3 g.) and refluxed for 5 hr. At the end of that period, selenium dioxide (0.6 g.) was again added and after continuing the reflux for a further period of 5 hr., the xylene solution was filtered from selenium and evaporated to dryness under reduced pressure. The solid residue (1.2 g.) was dissolved in a few milliliters of benzene and chromatographed by passage through a column of Brockmann alumina (30 g.) which was eluted with the same solvent. Evaporation of benzene left an almost colorless solid which on crystallizations from ethyl acetate–petroleum ether afforded IVa as colorless needles (1 g.; 64.7%), m.p. 140–141°, undepressed on admixture with an authentic specimen prepared earlier[2] by a different route.

6,7-Demethoxyisocoumarin (VIa).—A mixture of IVa (0.7 g.), N-bromosuccinimide (0.68 g.), and benzoyl peroxide (0.02 g.) in carbon tetrachloride (25 ml.) was refluxed, the reaction flask being kept close to an illuminated 60-watt lamp. The yellow color of the reaction mixture, which developed in the beginning disappeared after a 1.5-hr. reflux when benzoyl peroxide (0.02 g.) was again added and the reflux continued further for 1 hr. The cooled solution was filtered from succinimide and concentrated to a small bulk (copious evolution of hydrogen bromide). On the next day, the deposited solid was collected, almost dissolved in ethyl acetate, and filtered from a little insoluble unidentified compound, m.p. 237–238°. Most of the ethyl acetate was distilled (hydrogen bromide evolved) and petroleum ether added to give a paste of colorless crystals, m.p. 118–120°. Recrystallizations from ethyl acetate–petroleum ether gave VIa as needles (0.5 g.; 72%), m.p. 122–123° (lit.,[8] m.p. 121–122°). Since the pure isocoumarin gave positive Beilstein test, several crystallizations were necessary to obtain an analytical specimen, the melting point remaining unchanged.

Anal. Calcd. for $C_{11}H_{10}O_4$: C, 64.07; H, 4.8. Found: C, 64.2; H, 4.6.

Methyl 2-carbomethoxy-6-methoxy-4-methylphenylacetate (Ib) was prepared from 7-acetyl-6-methylisocoumaranone-4,5-dicarboxylic acid anhydride by way of 6-methylisocoumaranone-4-carboxylic acid as recorded previously,[9] but with following modifications: When the acid anhydride (10 g.) was boiled with hydroiodic acid (120 ml.; *d* 1.7) and red phosphorus (3 g.) for 7 hr., the cooled mixture deposited 6-methylisocoumaranone-4-carboxylic acid mixed with red phosphorus. On isolation with the aid of 2 *N* sodium carbonate the acid separated from ethanol in tiny crystals (6.5 g.), m.p. 259°. Methylation was then effected by simultaneous, but separate, dropwise addition of dimethyl sulfate (40 ml.) and 25% aqueous sodium hydroxide (50 ml.) to a well stirred solution of the acid (10 g.) in 25% sodium hydroxide solution (50 ml.) at such rates that there was a considerable rise of temperature and the mixture always remained strongly basic. After 1 hr. at room temperature it was refluxed for 2 hr., cooled, and filtered. Acidification of the filtrate precipitated the methoxy acid which crystallized from water in needles (9 g.), m.p. 208°. Esterified quantitatively with excess ethereal diazomethane, it furnished methyl 2-carbomethoxy-6-methoxy-4-methylphenylacetate (9.2 g.), m.p. 82° (lit.,[9] m.p. 82°).

2-Hydroxymethyl-6-methoxy-4-methylphenethyl Alcohol (IIb).—A solution of Ib (5.5 g.) in dry ether (100 ml.) was reduced with lithium aluminum hydride (2 g.) in dry ether (75 ml.) according to the procedure described above for the preparation of IIa. It was worked up by adding cautiously just enough water to the stirred reaction mixture to cause precipitation of a granular white solid which was filtered off and washed with dry ether. The combined filtrate and the washings was dried over anhydrous sodium sulfate and the ether evaporated to leave a white solid residue. Recrystallizations from ethyl acetate–petroleum ether furnished the alcohol (IIb) in colorless rectangular prisms (4 g.; 93%), m.p. 119°.

Anal. Calcd. for $C_{11}H_{16}O_3$: C, 67.3; H, 8.2. Found: C, 67.5; H, 7.9.

7-Methyl-5-methoxyisochroman (IIIb).—An intimate mixture of IIb (4 g.) and freshly fused potassium acid sulfate (5 g.) was heated for 1 hr. in an oil bath at 130–140°, the system being connected to an efficient water pump when most of the water distilled. The residue was next distilled under vacuum to yield IIIb as a colorless distillate (3 g.; 83%), b.p. 106–108°/0.5 mm; $n^{25}D$ 1.5447.

Anal. Calcd. for $C_{11}H_{14}O_2$: C, 74.15; H, 7.86. Found: C, 74.5; H, 7.5.

3,4-Dihydro-7-methyl-5-methoxyisocoumarin (IVb).—IIIb (1.5 g.) in xylene (20 ml.) was oxidized with selenium dioxide (1.5 g.) according to the procedure described above for the preparation of IVa. After chromatography, the benzene solution on evaporation left a mixture of oily unchanged material and yellow crystalline solid, which when washed with petroleum ether removed the oil. The solid residue was sublimed *in vacuo* (bath temp. 105–110°/1.25 mm.) to yield a colorless crystalline sublimate, m.p. 78–80°, which was recrystallized from ethyl acetate–petroleum ether to furnish IVb in cubes (0.5 g.; 31.3%), m.p. 80°.

Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68.7; H, 6.25. Found: C, 68.4; H, 5.8.

The unchanged isochroman (IIIb) (0.5 g.) was recovered from the petroleum ether washings.

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(10) All melting points are uncorrected. The petroleum ether used had b.p. 60–80°. Microanalyses by Drs. Weiler and Strauss, Oxford, and Dr. Gore, Bombay University.

(11) F. H. Howell and D. A. H. Taylor, *J. Chem. Soc.*, 4252 (1956).

7-Methyl-5-methoxyisocoumarin (VIb).—A mixture of IVb (0.22 g.), N-bromosuccinimide (0.22 g.), and benzoyl peroxide (0.002 g.) in carbon tetrachloride (6 ml.) was refluxed, the reaction flask being kept close to an illuminated 60-watt lamp as detailed above for the preparation of VIa. The yellow color, in this case, disappeared after 45 min. when more benzoyl peroxide (0.002 g.) was added and the reflux continued for a further period of 15 min. Succinimide was filtered off from the cooled solution and the filtrate evaporated (copious evolution of hydrogen bromide) to a thick oily residue, which from ethyl acetate–petroleum ether (ice chest) furnished VIb (0.17 g.; 78%) as colorless needles, m.p. 105–108°. A few recrystallizations from the same solvent gave the pure isocoumarin, m.p. 109° (lit.,[8] m.p. 108°). It can also be purified by vacuum sublimation.

Anal. Calcd. for $C_{11}H_{10}O_3$: C, 69.5; H, 5.3. Found: C, 69.7; H, 5.1.

Demethylation of a sample of VIb with hydroiodic acid at 130–140°/0.5 hr. and isolation in the usual way gave a product which was purified by vacuum sublimation to yield 5-hydroxy-7-methylisocoumarin, m.p. 162° (lit.,[8] m.p. 163°).

2-Hydroxymethyl-5,6-dimethoxyphenethyl Alcohol (IIc).—2-Carboxy-5,6-dimethoxyphenylacetic acid[12] (10 g.) was esterified with excess ethereal diazomethane (from 25 g. of *N*-nitrosomethylurea) in the usual way to give methyl 2-carbomethoxy-5,6-dimethoxyphenylacetate (Ic), which was purified by crystallizations from ethyl acetate–petroleum ether in colorless rectangular prisms (9.8 g.; 89%), m.p. 79°.

Anal. Calcd. for $C_{13}H_{16}O_6$: C, 58.20; H, 5.97. Found: C, 58.5; H, 6.2.

A solution of Ic (9 g.) in dry ether (100 ml.) was reduced with lithium aluminum hydride (2.5 g.) in anhydrous ether (75 ml.) and worked up according to the procedure described above for the preparation of IIb. Recrystallizations from ethyl acetate–petroleum ether afforded IIc (7 g.; 96%) as a mass of felted needles, m.p. 106°.

Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62.26; H, 7.5. Found: C, 62.6; H, 7.1.

5,6-Dimethoxyisochroman (IIIc).—An intimate mixture of IIIc (4 g.) and freshly fused potassium acid sulfate (4 g.) was heated for 1 hr. in an oil bath at 120°, the system being connected to an efficient water pump to remove most of the water formed during the reaction. Subsequent distillation *in vacuo* gave a colorless oil (3.1 g.; 89%), b.p. 120–125°/1.5 mm., which soon solidified to a mass of prismatic needles, m.p. 61–62°. A sample purified by vacuum sublimation melted at 62°.

Anal. Calcd. for $C_{11}H_{14}O_3$: C, 68.0; H, 7.2. Found: C, 68.3; H, 7.6.

3,4-Dihydro-5,6-dimethoxyisocoumarin (IVc).—A solution of chromium trioxide (4.8 g.) in water (4 ml.) and glacial acetic acid (16 ml.) was added dropwise with stirring to IIIc (2.9 g.) dissolved in glacial acetic acid (87 ml.), maintained at 30–35° by occasional external cooling the exothermic reaction with ice-water. After stirring for 1 hr. at room temperature, it was treated with an equal volume of water, extracted with chloroform (3 × 75 ml.), the extract washed with *N* sodium carbonate solution and water, and dried over anhydrous sodium sulphate. Evaporation of the chloroform left a residue of yellow needles which was purified by recrystallization from ethyl acetate–petroleum ether to yield IVc as colorless rectangular prisms (1.5 g.), m.p. 72–73°. An additional quantity (1.1 g.) of pure IVc was recovered by working up the mother liquor (total yield 2.6 g.; 81%).

Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63.4; H, 5.7. Found: C, 63.1; H, 5.5.

4-Bromo-3,4-dihydro-5,6-dimethoxyisocoumarin (Vc).—A mixture of IVc (1 g.), N-bromosuccinimide (0.98 g.), and benzoyl peroxide (0.01 g.) in carbon tetrachloride (25 ml.) was refluxed for 1 hr., close to an illuminated 60-watt lamp. More benzoyl peroxide (0.01 g.) was added and the reflux continued for a further period of 3 hr. The yellow color, which developed in the beginning, was not discharged at the end of the reaction. The cooled solution was filtered from succinimide which was washed with carbon tetrachloride, and the filtrate and the washings were combined and evaporated. Recrystallizations of the solid residue from ethyl acetate–petroleum ether furnished Vc (1.25 g.; 95%) as colorless irregular prisms, m.p. 128–129°.

Anal. Calcd. for $C_{11}H_{11}O_4Br$: C, 45.9; H, 3.8; Br, 27.8. Found: C, 46.38; H, 3.84; Br, 28.20.

5,6-Dimethoxyisocoumarin (VIc).—Vc (0.5 g.) in triethylamine (10 ml.) was refluxed for 15 hr. and the solid residue left after the evaporation of triethylamine, was triturated repeatedly with ice-cold 2 *N* hydrochloric acid followed by water. It was purified by vacuum sublimation (bath temp. 100–105°/1.5 mm.) and subsequent recrystallizations from ethyl acetate–petroleum ether to yield pure VIc as long fine needles (0.28 g.; 80%), m.p. 90°.

Anal. Calcd. for $C_{11}H_{10}O_4$: C, 64.07; H, 4.8. Found: C, 63.94; H, 4.88.

2-Hydroxymethyl-4,5-methylenedioxyphenethyl Alcohol (IId).—*p*-Toluenesulfonyl chloride (16 g.) was added in portions with stirring to 2-isonitroso-4,5-methylenedioxyindan-1-one[13] (9 g.) in 10% sodium hydroxide solution (160 ml.) at 40–45° and the solution maintained at that temperature for 30 min. It was then heated on water bath for 10 min., filtered from a little insoluble impurities, 10% aqueous sodium hydroxide (100 ml.) added, and refluxed for 10 hr. The cooled solution was acidified and the precipitate on recrystallization from a large volume of hot water furnished 2-carboxy-4,5-methylenedioxyphenylacetic acid (6 g.), m.p. 234° (lit.,[13] m.p. 236°).

The acid (6 g.) was esterified with excess ethereal diazomethane (from 15 g. of N-nitrosomethylurea) in the usual way to yield methyl 2-carbomethoxy-4,5-methylenedioxyphenylacetate (Id), which was recrystallized from ethyl acetate in colorless irregular prisms (5.4 g.; 80%), m.p. 95–96°.

Anal. Calcd. for $C_{12}H_{12}O_6$: C, 57.14; H, 4.76. Found: C, 57.4; H, 4.9.

A solution of Id (4 g.) in dry ether (100 ml.) was reduced with lithium aluminum hydride (1.2 g.) in anhydrous ether (75 ml.) and worked up as described above for the preparation of IIb. Recrystallizations from ethyl acetate–petroleum ether afforded IId (2.2 g.; 73%) in colorless prisms, m.p. 73°.

Anal. Calcd. for $C_{10}H_{12}O_4$: C, 61.2; H, 6.12. Found: C, 61.5; H, 5.8.

6,7-Methylenedioxyisochroman (IIId).—An intimate mixture of IId (3.2 g.) and freshly fused potassium acid sulfate (4 g.) was heated on water bath for 1 hr., the system being connected to an efficient water pump. Vacuum distillation of the residue yielded a colorless oil (b.p. 117–118°/1 mm.) which immediately solidified to a mass of tiny prismatic needles (2.8 g.; 94%), m.p. 87–88°.

Anal. Calcd. for $C_{10}H_{10}O_3$: C, 67.1; H, 5.6. Found: C, 67.4; H, 5.2.

3,4-Dihydro-6,7 methylenedioxyisocoumarin (IVd).—A solution of IIId (2 g.) in glacial acetic acid (60 ml.) was oxidized with chromium trioxide (3.2 g.) dissolved in water (1.4 ml.) and glacial acetic acid (5.6 ml.) at 30–35° according to the procedure described above for the preparation of IVc. The solid residue left after evaporation of the chloroform extract, on crystallizations from ethyl acetate–petroleum ether gave IVd as colorless prisms (1.2 g.; 56%), m.p. 127°. It can also be purified by vacuum sublimation.

Anal. Calcd. for $C_{10}H_8O_4$: C, 62.5; H, 4.16. Found: C, 62.8; H, 3.8.

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[12] M. Swaminathan and S. N. Chakravarti, *J. Indian. Chem. Soc.*, XI, 101 (1934).

[13] W. H. Perkin and R. Robinson, *J. Chem. Soc.*, 1084 (1907).

4-Bromo-3,4-dihydro-6,7-methylenedioxyisocoumarin (Vd).—After refluxing for 1 hr. a mixture of IVd (0.54 g.), N-bromosuccinimide (0.54 g.), and benzoyl peroxide (0.005 g.) in carbon tetrachloride (15 ml.), benzoyl peroxide (0.005 g.) was again added and the reflux continued for 2 hr. The mixture worked up as detailed above for the preparation of Vc. Recrystallizations of the product from ethyl acetate–petroleum ether (ice chest) yielded Vd in rosettes of needles (0.5 g.; 65%), m.p. 129°.

Anal. Calcd. for $C_{10}H_7O_4Br$: C, 44.2; H, 2.6; Br, 29.5. Found: C, 44.5; H, 3.0; Br, 29.8.

6,7-Methylenedioxideisocoumarin (VId).—Dehydrobromination of Vd (0.2 g.) with triethylamine (5 ml.), according to the procedure described above for the preparation of VIc, gave the product which on vacuum sublimation (bath temp., 150°/0.8 mm.) yielded white sublimate. Recrystallizations from ethyl acetate followed by methanol furnished pure VIc in rectangular prisms (0.1 g.; 71%), m.p. 168–169°.

Anal. Calcd. for $C_{10}H_6O_4$: C, 63.15; H, 3.16. Found: C, 63.13; H, 3.42.

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A New Synthesis of Ureas. IV. The Preparation of Unsymmetrical Ureas from Carbon Monoxide, Sulfur, and Amines

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The possible preparation of unsymmetrical ureas by the reaction of carbon monoxide, sulfur, and mixtures of amines has been investigated. The procedure may be most successfully used in the synthesis of 1,1-dialkyl-3-arylureas, and a series of these compounds was prepared and characterized.

An extension of a new method for the synthesis of urea from ammonia, carbon monoxide, and sulfur[3] to the preparation of symmetrical disubstituted ureas in high yields from aliphatic and aromatic amines was described recently.[4,5] The same procedure has proved to be satisfactory for the preparation of 1,1-dialkyl-3-arylureas, but is less advantageous for other classes of unsymmetrical ureas.

On the basis of experimental evidence, a mechanism has been proposed for the formation of urea from carbon monoxide, sulfur, and ammonia which involves the following steps[3]: initial formation of carbonyl sulfide from carbon monoxide and sulfur; condensation of carbonyl sulfide with ammonia to yield ammonium thiolcarbamate; decomposition of ammonium thiolcarbamate to cyanic acid and ammonium bisulfide; and the subsequent condensation of cyanic acid with ammonia to give urea. The recent isolation of thiolcarbamates from the reaction of dialkylamines with carbon monoxide and sulfur offers additional evidence for this mechanism.[6] If a mixture of two amines, for example, a primary and a secondary amine, were substituted for ammonia, the process could be represented by the following sequence:

$$\mathrm{S + CO \rightleftharpoons COS} \tag{1}$$

$$\mathrm{R_2NH + COS \rightleftharpoons R_2NCOSH{\cdot}R_2NH} \tag{2}$$

$$\mathrm{RNH_2 + COS \rightleftharpoons RNHCOSH{\cdot}RNH_2 \rightleftharpoons RNCO + RNH_2{\cdot}H_2S} \tag{3}$$

$$\mathrm{RNCO + RNH_2 \rightleftharpoons RNHCONHR} \tag{4}$$

$$\mathrm{RNCO + R_2NH \rightleftharpoons R_2NCONHR} \tag{5}$$

Because in this case the isocyanate intermediate can only be produced from the primary amine used in the reaction mixture, the possible urea products are the symmetrical disubstituted urea formed in (4) and the unsymmetrical trisubstituted urea obtained in (5). At the temperatures used in these syntheses, the equilibria in (4) and (5) favor the urea; therefore, the proportions of the two ureas in the product will be determined by the relative rates of reactions 4 and 5. The yield of the trisubstituted urea will be expected to be influenced by the nucleophilic character of the secondary amine, in comparison to that of the primary amine, and the presence or absence of steric hindrance in the secondary amine.

The situation becomes more complicated in the preparation of monosubstituted ureas when the mixed amines are a primary amine and ammonia. Both an organo isocyanate and cyanic acid may be considered as intermediates, each competing for the two amines. Attempts to prepare monosubstituted ureas from primary amines, ammonia, sulfur, and carbon monoxide led to mixtures containing the three possible products. Some of these results are summarized in Table I.

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