reserpine in 30 ml. of dry tetrahydrofuran. The reaction mixture was boiled under reflux for 3 hours, then cooled and decomposed with 10 ml. of water. After heating under reflux for one hour, inorganic salts were removed by filtration. The filtrate was freed from solvent under reduced pressure at 30° and the partially oily residue crystallized upon addition of ethanol. The crude reserpic alcohol weighed 240 mg. The material was recrystallized twice from dilute alcohol and formed long, silky prisms, m.p. 217–218° dec. The compound was dried for analysis 2 hours at room temperature and 0.05 mm. and contained one mole of water of crystallization; $[\alpha]^{26}D$ −66.7, −67.9; (*c* 0.780 in dimethylformamide). The compound appeared to be optically inactive in pyridine.

Anal. Calcd. for $C_{22}H_{30}N_2O_4 \cdot H_2O$: C, 65.32; H, 7.97; N, 6.93; OCH_3 (2), 15.33; act. H, 5 moles; mol. wt., 404. Found: C, 65.12, 65.40; H, 7.99, 7.99; N, 6.67; OCH_3 (2), 15.07; act. H, 4.82 moles; mol. wt., 409 ± 10 (electrometric titration, pK'_a 7.7).

For ultraviolet spectra see Fig. 1 and Table II. After drying in a pig at 100° *in vacuo:* weight loss calcd. 4.45. Found: 4.63.

Anal. Calcd. for $C_{22}H_{30}N_2O_4$: C, 68.37; H, 7.82. Found: C, 68.33; H, 8.00.

The hydrochloride of reserpic alcohol was recrystallized twice from methanol–ether and melted at 258–260° dec. It was dried for analysis 16 hours at 80° and 0.1 mm.

Anal. Calcd. for $C_{22}H_{30}N_2O_4 \cdot HCl$: N, 6.62; Cl, 8.38. Found: N, 6.61; Cl, 8.16.

The mother liquor from the first crystallization of reserpic alcohol was evaporated under reduced pressure and 30° and a small amount of an oily residue (110 mg.) obtained. This oil was dissolved in 5 ml. of dry pyridine and reacted with *p*-nitrobenzoyl chloride. After the usual work up, the *p*-nitrobenzoate of 3,4,5-trimethoxybenzyl alcohol was obtained. The same derivative, m.p. 143°, was obtained from an authentic sample of the alcohol.[20] The m.p., mixed m.p. and infrared spectra were identical.

Anal. Calcd. for $C_{17}H_{17}NO_7$: C, 58.79; H, 4.93; N, 4.03. Found: C, 58.78; H, 5.02; N, 4.01.

Synthesis of 2,3-Dimethyl-6-methoxyindole.—A solution of 2 g. (0.0145 mole) of 3-methoxyphenylhydrazine (b.p. 160–162° (13 mm.))[21] and 1 g. (0.0139 mole) of methyl ethyl ketone was boiled under reflux for 15 minutes. The mixture was then cooled in ice, removed from the ice-bath and saturated with dry hydrogen chloride for 17 minutes. During this operation the solution turned red, then dark brown and a copious crystalline precipitate appeared. The reaction mixture was then cooled in ice and allowed to stand for 15 minutes. The 2,3-dimethyl-6-methoxyindole was collected (1.15 g.) and washed thoroughly with dilute ice cold alcohol. Two recrystallizations from dilute alcohol afforded colorless, shiny plates, m.p. 142–143°.

Anal. Calcd. for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.20; H, 7.57; N, 7.92.

For ultraviolet spectra see Table I and Fig. 1, for infrared spectra see Fig. 2.

(20) Kindly supplied by Dr. E. R. Shepard, of these laboratories. The alcohol was prepared by $LiAlH_4$ reduction of the corresponding acid.

(21) W. O. Kermack, W. H. Perkin, Jr., and R. Robinson, *J. Chem. Soc.*, **119**, 1602 (1921).

INDIANAPOLIS 6, INDIANA

[CONTRIBUTION FROM THE NEW YORK STATE AGRICULTURAL EXPERIMENT STATION, CORNELL UNIVERSITY]

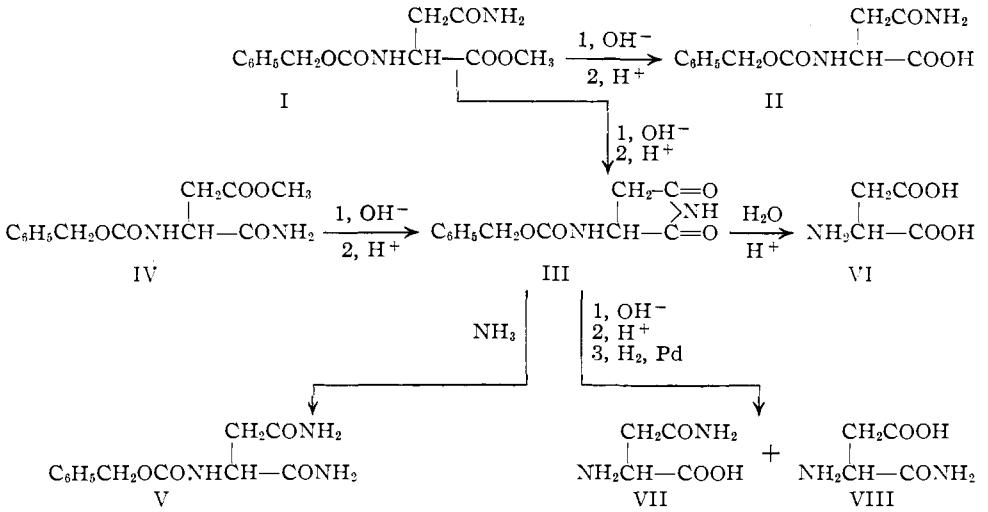
Imides from Asparagine and Glutamine[1]

BY ERNEST SONDHEIMER AND ROBERT W. HOLLEY

RECEIVED DECEMBER 22, 1953

Carbobenzoxy-L-aminosuccinimide (III) was obtained from carbobenzoxy-L-asparagine methyl ester by treatment with alkali. Hydrogenolysis of III gave L-aminosuccinimide (IX). Similar reactions take place in the glutamine series. The properties of these new compounds are described.

In the course of investigations of the synthesis of peptides of asparagine and glutamine, we had occasion to attempt to saponify carbobenzoxy-L-asparagine methyl ester (I). Contrary to expectations, the isolated material was not carbobenzoxy-L-asparagine (II), m.p. 165°, but a mixture, containing as its major component a compound (III), m.p. 79–81°, pK = 9.1 in aqueous methanol. Attempted saponification of carbobenzoxy-L-isoaspar-

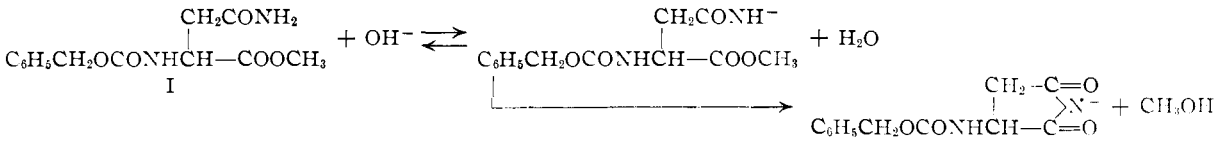


(1) Journal Paper No. 958, New York State Agricultural Experiment Station. This investigation was supported in part by a research grant, G-3435, from the National Institutes of Health, Public Health Service.

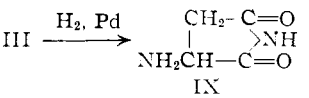
agine methyl ester (IV) also gave III as the major product.

Efforts to identify III led to the conclusion that the compound is carbobenzoxy-L-aminosuccinimide. The elemental analyses and amide-nitrogen determination are in agreement with this structure. This structure explains the weakly acidic properties of III,[2] as well as the fact that the same product is obtained from carbobenzoxy-L-asparagine methyl ester and carbobenzoxy-L-isoasparagine methyl ester. Conclusive evidence for the imide structure is furnished by the reactions of III. With excess aqueous ammonia, III gives carbobenzoxyaspartic acid diamide (V). With refluxing hydrochloric acid III gives L-aspartic acid (VI). Prolonged treatment of III with aqueous alkali, followed by hydrogenolysis of the reaction mixture, yields a mixture of asparagine (VII) and isoasparagine (VIII).

The formation of an imide from an amido ester is not without precedent, since de Mouilpied and Rule[3] obtained succinimide in low yield by treatment of methyl succinamate with alkali. A possible mechanism for imide formation from carbobenzoxy-L-asparagine methyl ester is given in the following equations. Hydrolysis of I to give carbobenzoxy-L-asparagine would, of course, be a competing reaction.



Hydrogenolysis of carbobenzoxy-L-aminosuccinimide (III) yielded L-aminosuccinimide (IX). Previous unsuccessful attempts to prepare this compound have been described.[4,5] L-Aminosuccinimide is a nicely crystalline compound, and is



IX

stable at room temperature for at least 2 months. It is soluble in water and methanol, and gives a brownish color with ninhydrin reagent and an extremely weak biuret test. Electrometric titration shows the presence of a weakly acidic group with pK = 9.0, the imide group, and a weakly basic group with pK = 5.9, the amino group. In aqueous solution L-aminosuccinimide is slowly converted to asparagine and isoasparagine as well as polymeric products. Whether this reactivity will make the imide and its derivatives useful synthetic intermediates remains to be investigated.

Since carbobenzoxy-L-glutamine methyl ester differs from carbobenzoxy-L-asparagine methyl ester only by the presence of an added methylene group, it was considered very probable that the glutamine derivative would also give an imide on treatment with alkali. This expectation was realized by the isolation of carbobenzoxy-DL-α-aminoglutarimide from the ester using sodium methoxide in benzyl alcohol. Only racemized preparations have been obtained thus far. Since aqueous alkali hydrolyzes glutarimides more rapidly than succinimides,[6] it has not been possible to isolate carbobenzoxy-α-aminoglutarimide from aqueous systems. Evidence for the intermediate formation of the imide in aqueous systems has been obtained, since alkaline hydrolysis of carbobenzoxy-L-glutamine methyl ester, followed by hydrogenolysis of the reaction mixture yielded a mixture of glutamine and isoglutamine. Similar results were obtained starting with carbobenzoxy-L-isoglutamine methyl ester. Hydrogenolysis of carbobenzoxy-α-aminoglutarimide has not as yet yielded pure α-aminoglutarimide. The latter compound appears to be less stable than L-aminosuccinimide.

That these imides may play a role in metabolic processes is being considered. In this connection it may be pointed out that a glutarimide derivative, actidione, has been isolated from *Streptomyces griseus* by Kornfeld, *et al.*[2] Furthermore, the isolation of L-pyrrolidonyl-α-L-glutaminyl-L-glutamine from a marine alga by Dekker, Stone and Fruton[7] is rather suggestive, since α-aminoglutarimide might be a precursor of this peptide. There is also the possibility that the imides might be intermediates of some of the naturally occurring heterocyclic nitrogen compounds.

Experimental[8]

Carbobenzoxy-L-aminosuccinimide.—To 1.120 g. of carbobenzoxy-L-asparagine methyl ester[9] (4.0 mmoles), 3.2 ml. of 1.27 N sodium hydroxide was added, the mixture was stirred for 5 minutes and the solution acidified with 1 N hydrochloric acid. This caused the immediate precipitation of crystalline crude product. After storing the mixture 2 hours at 0° the precipitate was filtered off, washed with 5 ml. of water and taken up in 6 ml. of ethyl acetate. The ethyl acetate solution was extracted with 2 ml. of *p*H 7.0 phosphate buffer, the supernatant removed, and the aqueous phase extracted with 4 ml. of ethyl acetate. The combined ethyl acetate extracts were again treated with 1 ml. of *p*H 7.0 buffer, dried over anhydrous sodium sulfate and concentrated *in vacuo* to about one third the original volume. Dropwise addition of hexane caused the precipitation of crystalline product. After the further addition of 10 ml. of hexane and storage at 0° overnight, the mixture yielded 765 mg. (77%) of carbobenzoxy-L-aminosuccinimide, m.p. 79–81°, $[\alpha]^{24}D$ −43° (c 1, 95% ethanol). The compound was recrystallized from ethyl acetate and hexane before

(2) Succinimide has a pK = 9.35. Glutarimide has a pK = 11.2. E. C. Kornfeld, R. G. Jones and T. V. Parke, THIS JOURNAL, **71**, 150 (1949).

(3) A. T. de Mouilpied and A. Rule, *J. Chem. Soc.*, **91**, 176 (1907).

(4) E. Fischer and E. Koenigs, *Ber.*, **37**, 4585 (1904).

(5) F. C. Steward and J. F. Thompson, *Nature*, **169**, 739 (1952). The results described in the present paper demonstrate conclusively that Steward and Thompson's proposal of an imide structure for asparagine is untenable since the properties of an aqueous solution of asparagine and one of aminosuccinimide are not similar. (*Cf.* L. Katz, R. A. Pasternak and R. B. Corey, *ibid.*, **170**, 1066 (1952); S. J. Leach and H. Lindley, *ibid.*, **171**, 1062 (1953); F. C. Steward and J. F. Thompson, *ibid.*, **171**, 1063 (1953)).

(6) S. S. G. Sircar, *J. Chem. Soc.*, 600, 1252 (1927).

(7) C. A. Dekker, D. Stone and J. S. Fruton, *J. Biol. Chem.*, **181**, 719 (1949).

(8) All melting points were determined on a microscope hot-stage and are corrected. Analyses are by Dr. G. Weiler and Dr. F. B. Strauss, Oxford, England.

(9) M. Bergmann and L. Zervas, *Ber.*, **65**, 1192 (1932).

analysis. However, the low carbon analysis indicates that the compound is not analytically pure.

Anal. Calcd. for $C_{12}H_{12}N_2O_4$: C, 58.05; H, 4.87; N, 11.29; amide-N, 5.65. Found: C, 57.29; H, 5.17; N, 11.25; amide-N, 5.50.

Carbobenzoxy-L-aminosuccinimide, $[\alpha]^{24}D$ −43° (*c* 1, 95% ethanol), could also be prepared in 70% yield from carbobenzoxy-L-isoasparagine methyl ester by the above procedure. Carbobenzoxy-L-asparagine methyl ester yielded 70% carbobenzoxy-L-aminosuccinimide, $[\alpha]^{24}D$ −43° (*c* 1, 95% ethanol) with sodium methoxide in absolute methanol. Apparently this reaction is complicated by reaction of the carbobenzoxy group since the odor of benzyl alcohol could be detected during work up of the reaction mixture.

A solution of 248 mg. (1 mmole) of carbobenzoxy-L-aminosuccinimide in 1.5 ml. of 2 *N* hydrochloric acid was refluxed for 4 hours, the mixture was cooled, extracted with benzene and the *p*H was adjusted to 3.4 with concentrated sodium hydroxide. L-Aspartic acid was obtained in 72% yield, $[\alpha]^{23}D$ +24.1° (*c* 1, 3 *N* hydrochloric acid).

Carbobenzoxyaspartic Acid Diamide.—To 138 mg. of carbobenzoxy-L-aminosuccinimide 0.5 ml. of 28% aqueous ammonia was added. After a few minutes crystals started to precipitate and the mixture was filtered after storage at room temperature overnight. The yield of crude product was 122 mg. (83%), m.p. 209–217° dec. raised to 219–223° dec. after recrystallization from 3 ml. of dimethylformamide. A mixture of this preparation with carbobenzoxyaspartic acid diamide prepared from carbobenzoxy-L-asparagine methyl ester and aqueous ammonia did not depress the melting point.

Anal. Calcd. for $C_{12}H_{15}N_3O_4$: N, 15.8. Found: N, 15.6.

Hydrolysis of Carbobenzoxy-L-asparagine Methyl Ester.—Since the *pK* values of carbobenzoxy-L-asparagine and carbobenzoxy-L-isoasparagine are approximately 4 units lower than that of carbobenzoxy-L-aminosuccinimide, an estimate of the concentration of these compounds during hydrolysis may be obtained by electrometric titration. Carbobenzoxy-L-asparagine methyl ester, 280 mg. (1 mmole) was suspended in 1.21 ml. of methanol at 18° and 0.79 ml. of 1.27 *N* sodium hydroxide was added with stirring. The ester had dissolved completely in 3 minutes. The temperature was maintained at 18° and 0.20-ml. aliquots were removed periodically and added at once to 1 ml. of 90% methanol containing 0.10 mmole of hydrochloric acid. The maximum concentration of imide was found in the aliquot removed after 3 minutes, which contained 90% imide and 10% stronger acids. Hydrolysis of the imide was rather slow, since 10.5 hours were necessary for half of the imide to be hydrolyzed.

Chromatographic analysis of an equimolar aqueous solution of sodium hydroxide and carbobenzoxy-L-asparagine methyl ester which had been stored for 6 days at room temperature, then neutralized and hydrogenated with palladium black, gave spots whose R_f values corresponded with those for pure L-asparagine and L-isoasparagine. No evidence for the presence of L-aspartic acid was obtained. The R_f values found at 25° for L-aspartic acid, L-asparagine and L-isoasparagine are 0.2, 0.15 and 0.2 in the *n*-butyl alcohol system, and 0.2, 0.45 and 0.4, respectively, in the phenol system. Samples were chromatogramed on Whatman No. 1 paper using *n*-butyl alcohol, acetic acid, water (4:1:5) and phenol saturated with water. Isoasparagine gives a violet spot with ninhydrin under the same conditions that asparagine gives a brown spot.

L-Aminosuccinimide.—Bubbling hydrogen through a mixture of 248 mg. (1 mmole) of carbobenzoxy-L-aminosuccinimide, 50 mg. of palladium black and 10 ml. of methanol at room temperature for two hours, filtering and concentrating the filtrate *in vacuo*, resulted in the formation of 105 mg. (92%) of crude L-aminosuccinimide. The latter was recrystallized in 64% yield by dissolving it in 1 ml. of dimethylformamide, centrifuging, adding 5 ml. of ether to the supernatant, and storing overnight at 0°. The compound melts with decomposition at approximately 144°, $[\alpha]^{24}D$ −77° (*c* 1, methanol). The R_f values of L-aminosuccinimide in *n*-butyl alcohol, acetic acid and water (4:1:5) and phenol saturated with water are 0.3 and 0.9, respectively.

Anal. Calcd. for $C_4H_6N_2O_2$: C, 42.10; H, 5.30; N, 24.6; neut. equiv., 114. Found: C, 42.34; H, 5.28; N, 24.85; neut. equiv., 118 (titrated with 0.1 *N* hydrochloric acid).

On the basis of the elemental analyses alone definite structure assignment is not possible since the diketopiperazine of asparagine would give the same analyses as aminosuccinimide. However from the chemical and physical properties, the possibility that the compound is the diketopiperazine can be ruled out.

L-Aminosuccinimide decomposes in aqueous solution. All the aminosuccinimide had been destroyed by heating a 2% solution for 90 minutes at 80°. Chromatographic analysis indicated the formation of asparagine and isoasparagine. The solution gave a positive biuret test and after standing overnight at 0° a small amount of crystalline material had precipitated which was insoluble in aqueous hydrochloric acid and may be the diketopiperazine of asparagine. Storage of a 1% solution of L-aminosuccinimide in *p*H 7.0 phosphate buffer at 37° for 14 hours caused the destruction of at least 90% of the L-aminosuccinimide.

Carbobenzoxy-L-glutamine Methyl Ester.—To 21.5 g. (0.076 mole) of carbobenzoxy-L-glutamine[10] in 120 ml. of anhydrous ethanol an ethereal solution of diazomethane[11] was added with cooling until a permanent yellow color was obtained. The mixture was stored in an ice-bath for 30 minutes and the excess diazomethane was then decomposed with acetic acid. Crystallization of the product was completed during overnight storage at 0°. The mixture was filtered and the precipitate was washed with ether and dried. The yield of crude material was 14 g., m.p. 140–141°, unchanged by recrystallization from methanol, $[\alpha]^{23}D$ −19.4° (*c* 1, methanol). Concentration of the filtrate *in vacuo* gave 5.5 g. of partially crystalline material which after two recrystallizations from methanol yielded 2.3 g., m.p. 139–140°, making the total yield 72%.

Anal. Calcd. for $C_{14}H_{18}N_2O_5$: C, 57.14; H, 6.16; N, 9.52; OCH_3, 10.58; NCH_3, 0.00; sapon. equiv., 294. Found: C, 57.17; H, 5.97; N, 10.14; OCH_3, 10.2; NCH_3, 0.4; sapon. equiv., 287.

Carbobenzoxy-L-isoglutamine Methyl Ester.—To 0.70 g. of finely ground carbobenzoxy-L-isoglutamine[10] an excess of an ethereal solution of diazomethane was added and the mixture held at room temperature for 30 minutes. Then the excess diazomethane was decomposed with acetic acid and the mixture was filtered. Recrystallization of the precipitate from 50% aqueous methanol yielded 0.22 g. of ester, m.p. 116–120°, raised to 118–120° by a second recrystallization, $[\alpha]^{24}D$ −5.7 (*c* 1, methanol).

Anal. Calcd. for $C_{14}H_{18}N_2O_5$: N, 9.52. Found: N, 9.50.

Carbobenzoxy-α-aminoglutarimide.—To a solution of 162 mg. (3 mmoles) of sodium methoxide in 1.5 ml. of benzyl alcohol, 882 mg. (3 mmoles) of carbobenzoxy-L-glutamine methyl ester was added, and a vacuum applied for 20 minutes. Then 0.3 ml. of acetic acid was added followed by 10 ml. of ethyl acetate. The mixture was filtered and the filtrate concentrated *in vacuo* to about 2 ml. The product was precipitated by the addition of 2.5 ml. each of benzene and hexane and the mixture was stored at 0° overnight. Filtration yielded 340 mg. of product, 43%, m.p. 122–123°. Recrystallization from 6 ml. of warm ethyl acetate yielded 296 mg. of carbobenzoxy-α-aminoglutarimide, m.p. 122–124°. Further recrystallizations did not raise the melting point. In a larger batch, in which 15 mmoles of reagents in 5 ml. of benzyl alcohol were used, the yield was raised to 56%. A solution of the compound in aqueous methanol had a *pK* above 11.[2] A 1% solution of this carbobenzoxy-α-aminoglutarimide in methanol was optically inactive. Hydrolysis of the imide to glutamic acid in 6 *N* hydrochloric acid also yielded an optically inactive solution.

Anal. Calcd. for $C_{13}H_{14}N_2O_4$: C, 59.53; H, 5.33; N, 10.7; amide-N, 5.35. Found: C, 59.40; H, 5.27; N, 10.85; amide-N, 5.33.

Alkaline Hydrolysis and Hydrogenolysis of Carbobenzoxy-L-glutamine Methyl Ester and Carbobenzoxy-L-isoglutamine Methyl Ester.—A solution of glutamine and isoglutamine was obtained on alkaline hydrolysis and hydrogenolysis of carbobenzoxy-L-glutamine methyl ester or carbobenzoxy-L-isoglutamine methyl ester. Hydrogenolysis of carbobenzoxy-L-isoglutamine and carbobenzoxy-L-gluta-

(10) H. K. Miller and H. Waelsch, *Arch. Biochem. Biophys.*, **35**, 176 (1952).

(11) F. Arndt, "Organic Syntheses," Coll. Vol. 2, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 165.

mine gave pure L-isoglutamine and L-glutamine, respectively. It may therefore be concluded that the isolation of a mixture of glutamine and isoglutamine from either ester after treatment with alkali is due to the intermediate formation of carbobenzoxy-α-aminoglutarimide.

The esters were dissolved in one equivalent of aqueous sodium hydroxide, stored at room temperature for 2 hours, neutralized with 1 *N* hydrochloric acid, and hydrogenated at room temperature with palladium black. The chromatographic analysis was carried out on Whatman No. 1 paper, using the solvent systems *n*-butyl alcohol, acetic acid, water (4:1:5) and phenol saturated with water.

The R_f values for the components of the hydrolyzed and hydrogenated preparations corresponded with those found for pure L-glutamine and L-isoglutamine. Evidence for the formation of traces of L-glutamic acid was also obtained. The R_f values found at 25° for L-glutamic acid, L-glutamine and L-isoglutamine are 0.25, 0.15 and 0.25 in the *n*-butyl alcohol system and 0.25, 0.6 and 0.6, respectively, in the phenol system.

GENEVA, NEW YORK

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

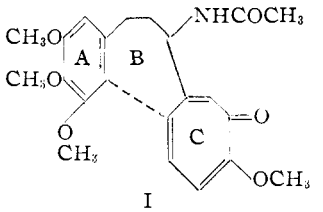
Synthetic Studies on the Colchicine Problem. The Preparation and Properties of Some Styryltropolones[1]

BY D. S. TARBELL, RICHARD F. SMITH AND V. BOEKELHEIDE

RECEIVED DECEMBER 21, 1953

The condensation of benzaldehyde, and of its 2-nitro, 2-acetamino and 3,4,5-trimethoxy derivatives, with α-carboxy-β-carboxymethyltropolone in the presence of acetic anhydride and triethylamine proceeds with the liberation of carbon dioxide. The products are the corresponding α-carboxy-β-styryltropolones, usually mixed with the O-acetyl derivatives. These compounds have been separated and characterized. The *o*-nitrostyryltropolone has been reduced by hydrazine–Raney nickel to the amino compound, which on diazotization and treatment with copper powder fails to cyclize. It is found from infrared and cyclization studies that, contrary to the usual results, the Perkin–Oglialoro reaction between the benzaldehydes studied and α-carboxy-β-carboxymethyltropolone yields only the *trans* isomers.

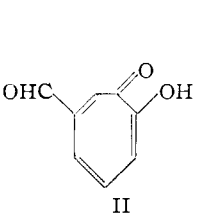
Most of the approaches to the synthesis of colchicine (I) which have been described so far[2] have projected the formation of rings A and B, followed by the elaboration of the tropolone ring C either by cyclization, or by introduction of the necessary oxygen functions and unsaturation into a relatively saturated seven-membered ring C.



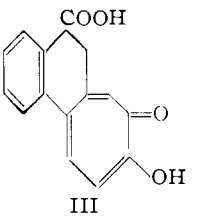
I

It occurred to us that a promising alternative scheme would be the formation of a compound containing an aromatic ring (A) connected to a tropolone ring (C) by a three-carbon chain, with an amino group in the one ring or the other, so situated that the bond between rings A and C (indicated with a dotted line in structure I) could be established by application of the Pschorr reaction. The present paper describes some model experiments designed to test the feasibility of this synthetic scheme.

Thus, β-formyltropolone[3] (II) might be condensed with oxindole, and the resulting product treated by the Windaus modification[4] of the Pschorr

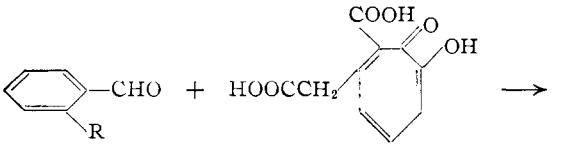


II

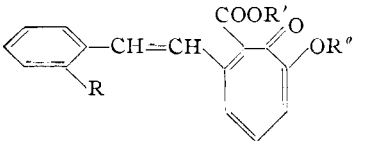


III

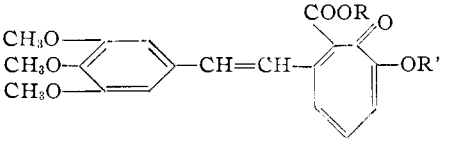
cyclization to form the tricyclic tropolone III. However, the much greater accessibility of α-carboxy-β-carboxymethyltropolone[3] (IV) suggested the investigation of the condensation of aromatic aldehydes with the active methylene group of IV.



IV



Va, R = NO_2; R′ = R″ = H
Vb, R = NO_2; R′ = H, R″ = $COCH_3$
Vc, R = NO_2; R′ = R″ = CH_3
Vd, R = NH_2; R′ = R″ = H
Ve, R = $NHCOCH_3$; R′ = R″ = H
Vf, R = R′ = R″ = H
Vg, R = R′ = H; R″ = $COCH_3$



VIa, R = R′ = H
VIb, R = H; R′ = $COCH_3$
VIc, R = R′ = CH_3

(1) This research was aided by a grant from the National Cancer Institute of the National Institutes of Health, Public Health Service.

(2) For example: H. Rapoport and J. E. Campion, THIS JOURNAL, **73**, 2239 (1951); C. D. Gutsche and K. L. Seligman, *ibid.*, **75**, 2579 (1953); P. D. Gardner and W. J. Horton, *ibid.*, **75**, 4976 (1953); A. G. Anderson, Jr., and H. F. Greef, *ibid.*, **74**, 5203 (1952); E. Ott and D. S. Tarbell, *ibid.*, **74**, 6266 (1952); G. A. Page and D. S. Tarbell, *ibid.*, **75**, 2053 (1953); A. Eschenmoser and H. H. Rennhard, *Helv Chim. Acta*, **36**, 290 (1953); V. Boekelheide and F. C. Pennington, THIS JOURNAL, **74**, 1558 (1952).

(3) R. D. Haworth and J. D. Hobson, *J. Chem. Soc.*, 561 (1951).

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