3-Hydroxymethylene oxindole[18] (1.6 g., 0.01 mole) and 1.5 g. (0.01 mole) of *o*-aminophenylacetamide were dissolved in 10 ml. of ethyl alcohol and the solution was re-

fluxed on the steam-bath for 15 minutes. Within that time a copious yellow precipitate was obtained. One recrystallization from ethyl alcohol gave 1.0 g. of yellow crystals, m.p. 227°. This substance gave no depression in melting point when mixed with XVIII and their infrared absorption spectra were virtually superimposable.

(18) E. Wenkert, N. K. Bhattacharyya, T. L. Reid and T. H. Stevens, *J. Am. Chem. Soc.*, **78**, 797 (1956).


An Unusual Base-catalyzed Cyclization

BY JOHN W. SCHULENBERG AND S. ARCHER

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The reaction between N-benzoyl-*o*-carbomethoxy-*o*'-(carbomethoxymethyl)-diphenylamine (XIV) and sodium methoxide gave 3-benzoyl-1-(*o*-carbomethoxyphenyl)-oxindole (XX) and a related indole, probably 1-(*o*-carbomethoxyphenyl)-2-phenyl-3-indolecarboxylic acid (XXXV), instead of the expected Dieckmann product XVII. Similarly, methyl *o*-(N-benzoylanilino)-phenylacetate (XXVIII) furnished 3-benzoyl-1-phenyloxindole (XXIX) and methyl 1,2-diphenyl-3-indolecarboxylate (XXXI), the structures of which were proved by independent syntheses.

In our previous paper,[1] we reported that treatment of *o*-(N-benzoylanilino)-phenylacetyl chloride (I) with aluminum chloride yielded 1-phenyloxindole (II) instead of the desired dihydrodibenzazepinone (III). Astill and Boekelheide had encountered the same problem in attempting to prepare a tetrahydrobenzazepinone. They finally synthesized the desired product (VI) by Dieckmann ring closure of the appropriate diester IV.[2] Similarly, Proctor and Thomson converted the analogous tosyl derivative V into VII by the Dieckmann reaction, previous attempts to prepare an azepinone by Friedel–Crafts and acyloin reactions having failed.[3] It therefore appeared that the most promising route to III was *via* cyclization of a suitable diester.

I → II   III

IV, R = CH₃
V, R = *p*-C₇H₇SO₂

VI, R = CH₃
VII, R = *p*-C₇H₇SO₂
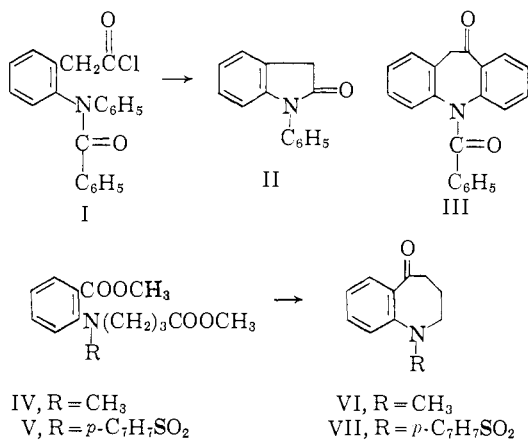
One of the best methods for preparing unsymmetrically substituted diphenylamines is the Chapman rearrangement.[4] While two imino-ethers, XII and XVI, could give the desired product XIV, only the former would be expected to rearrange smoothly. The imino-ether derived from methyl

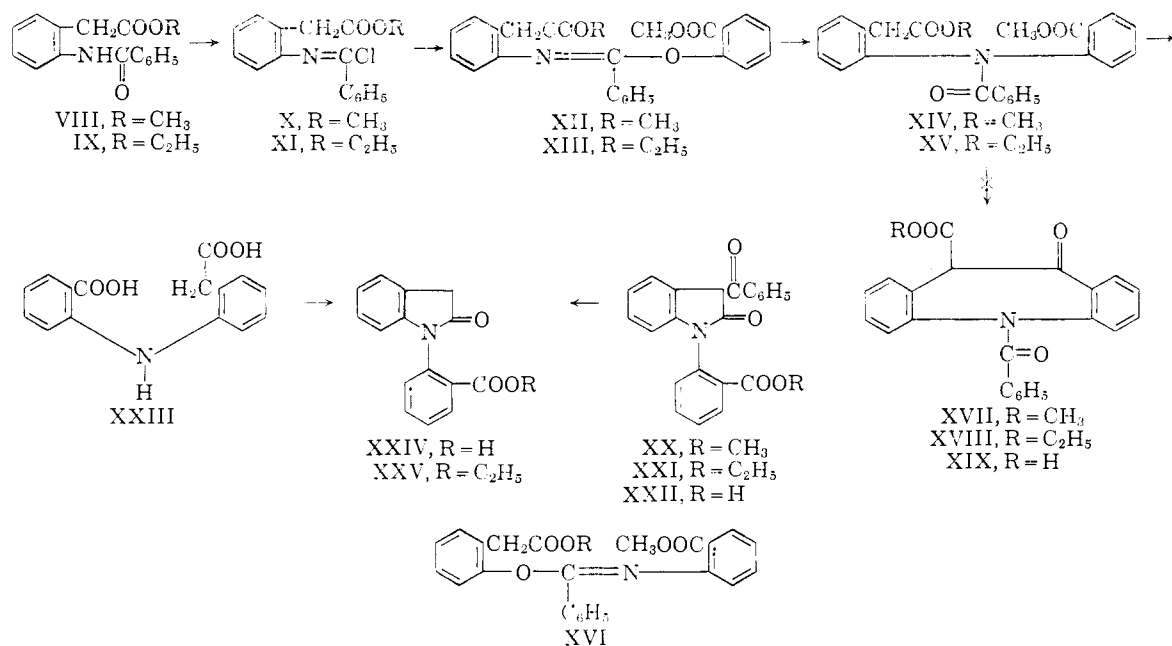(1) J. W. Schulenberg and S. Archer, *J. Am. Chem. Soc.*, **82**, 2035 (1960).

(2) B. D. Astill and V. Boekelheide, *ibid.*, **77**, 4079 (1955).

(3) G. R. Proctor and R. H. Thomson, *J. Chem. Soc.*, 2302, 2312 (1957).

(4) (a) A. W. Chapman, *ibid.*, **127**, 1992 (1925); (b) F. Möller in "Methoden der Organische Chemie," Band XI/1, Vierte Auflage, Georg Thieme Verlag, Stuttgart, pp. 910–913; (c) K. B. Wiberg and B. I. Rowland, *J. Am. Chem. Soc.*, **77**, 2205 (1955).

salicylate and benzanilimino chloride has been reported to rearrange in high yield to methyl N-benzoyl-N-phenylanthranilate[5] while the higher homolog XXVI prepared from methyl *o*-hydroxyphenylacetate gave a mixture containing the normal product and a compound (XXVII) resulting from a competing base-catalyzed cyclization.[1] Although a base-catalyzed reaction of XII to methyl salicylate and methyl 2-phenyl-3-indolecarboxylate is conceivable, it would not be expected to proceed at a rate sufficient to compete with the normal Chapman rearrangement which is accelerated by *meta*-directing groups *ortho* to the ether linkage.[4]

Methyl *o*-benzamidophenylacetate (VIII)[6] was therefore converted into the imino-chloride X. This was treated with the sodium salt of methyl salicylate to furnish the imino-ether XII in good yield. Pyrolysis of XII then afforded the desired diester XIV, apparently uncontaminated by abnormal Chapman products. The analogous ethyl ester XV was prepared similarly *via* IX, XI and XIII.

When the dimethyl ester XIV was treated with sodium methoxide in boiling benzene or toluene, 3-benzoyl-1-(*o*-carbomethoxyphenyl)-oxindole (XX) was obtained instead of the desired β-ketoester (XVII). When the corresponding ethyl ester XV was treated with sodium ethoxide in toluene, the homologous oxindole XXI was obtained. Compounds XX and XXI undoubtedly exist largely in the enolic form. Both cyclization products gave strong ferric chloride tests and had infrared spectra compatible with both the azepinone and oxindole structures.

When the ethyl ester XXI was refluxed for two hours with 5% aqueous potassium hydroxide, a dibasic acid was obtained. This was shown to be *o*-(2-carboxyanilino)-phenylacetic acid (XXIII) by its identity with material obtained by vigorous alkaline hydrolysis of our Chapman product (XIV). It is not surprising that the benzoyl group in XXI is cleaved readily by base, followed by saponification and ring-opening. However, the formation of XXIII can also be rationalized in terms of struc-

(5) M. M. Jamison and E. E. Turner, *J. Chem. Soc.*, 1954 (1937).

(6) P. W. Neber, *Ber.*, **55**, 826 (1922).

ture XVIII. Here, the strain which would exist in the seven-membered ring would tend to favor reversal of the Dieckmann reaction over simple saponification of the ester. The ring-opened intermediate then would be hydrolyzed readily to XXIII.

Hydrolysis of either XX or XXI with hydrobromic acid in aqueous acetic acid also resulted in cleavage of the benzoyl group. The product, 1-(o-carboxyphenyl)-oxindole (XXIV), was identical with authentic material prepared by acid-catalyzed cyclization of the dibasic acid XXIII. Hydrolysis of XXI with HCl in ethanol–water–dioxane furnished the corresponding ethyl ester XXV. Although these results could not rule out the azepinone structure, it seems more likely that, had we actually had XVIII, acid hydrolysis would have given either III or its debenzoylation product.

Hydrolysis of XX with potassium carbonate in aqueous methanol successfully saponified the ester group without affecting the rest of the molecule. The product XXII was a stable compound which gave a strong ferric chloride test. No evolution of carbon dioxide occurred when the acid was heated to 360°. Furthermore, decarboxylation did not occur in concentrated sulfuric acid even at 250°. Therefore, the azepinone structure XIX is ruled out, since this material would certainly lose carbon dioxide under such extreme conditions. Once the azepinone structures are discarded it is apparent that the cyclizations proceeded abnormally and that the oxindoles XX and XXI were formed. The following mechanism can explain the oxindole formation. The initially formed anion XIVa attacks the amide carbonyl rather than the carbomethoxy group as in the usual Dieckmann reaction. The resulting intermediate XIVb then opens to XIVc which can easily reclose with displacement of alkoxide ion to give the product XX. The first part of this reaction scheme is quite unusual in that an amide acts as an acylat-

ing agent in preference to an ester. This behavior is due chiefly to the severe strain which would exist in the azepinone XVII in contrast to the relatively strain-free five-membered rings in XIVb and XX. Furthermore, since XIV is an amide derived from a non-basic amine which yields a fairly stable anion (XIVc), acylation by the amide group is facilitated. It is interesting to note that these postulated steps for oxindole formation are completely analogous to the reaction scheme proposed for the abnormal, base-catalyzed Chapman rearrangement of N-phenylbenzimino o-(carbomethoxymethyl)-phenyl ether (XXVI) to 3-benzanilimino-2(3H)-benzofuranone (XXVII).[1]
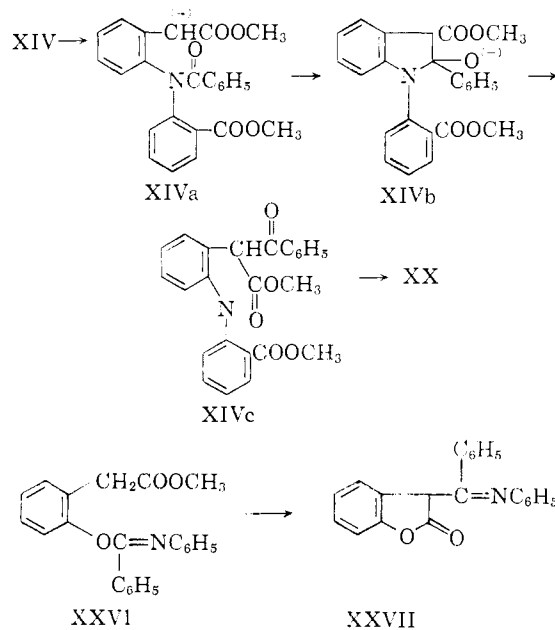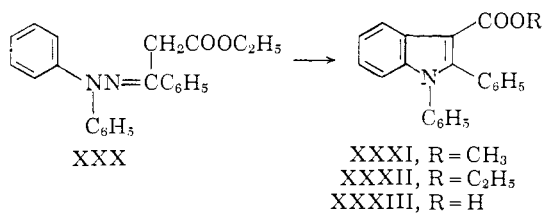

While the oxindole structures are compatible with the analytical, spectral and hydrolytic results,

one possible discrepancy remained. According to the above reaction scheme, the ethyl ester XV should yield a methyl ester (XX), whereas the actual product was XXI. Therefore, the dimethyl ester XIV was treated with sodium ethoxide in toluene. The product was the ethyl ester XXI. Transesterification occurred readily under our reaction conditions and the above reaction scheme is possible.

If the above mechanism is correct, the aromatic carbomethoxy group in XIV is superfluous and methyl o-(N-benzoylanilino)-phenylacetate (XXVIII) should similarly be converted by base into an oxindole. This material had previously been synthesized by Chapman rearrangement of XXVI; it was treated with sodium methoxide in boiling benzene. A product was obtained which was shown to be the expected 3-benzoyl-1-phenyloxindole (XXIX) by comparison with authentic material prepared from 1-phenyloxindole (II) and ethyl benzoate.

XXVIII → XXIX ↓ II
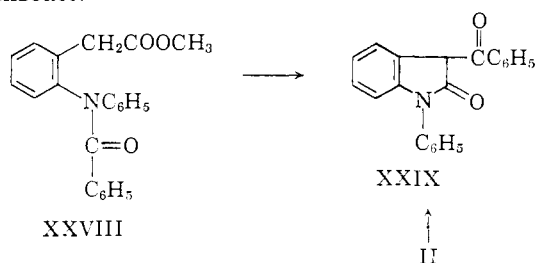
In the reactions of XIV, XV and XXVIII with base, small amounts of relatively high-melting by-products were formed. None of these gave a positive ferric chloride test and all three had ultra-violet spectra which excluded the oxindole structure. It appeared likely that these by-products might be indoles derived from the postulated intermediates such as XIVb by (formal) loss of hydroxide ion.[7] The material obtained from XXVIII would be methyl 1,2-diphenyl-3-indolecarboxylate (XXXI), a structure compatible with our analytical and spectral data. Accordingly, an independent synthesis of XXXI was carried out. Ethyl benzoylacetate was treated with N,N-diphenylhydrazine and the product XXX converted into XXXII via the Fischer indole synthesis. Saponification gave the acid XXXIII[8] which was treated with thionyl chloride, then methanol, to yield authentic methyl ester XXXI. This was shown

XXX → XXXI, R = CH₃
XXXII, R = C₂H₅
XXXIII, R = H

to be identical with the by-product from XXVIII by melting point, mixed melting point and spectra.

It appeared possible that 3-benzoyl-1-phenyloxindole (XXIX) might be converted into the indole XXXI by treatment with base. However, refluxing a xylene solution of XXIX with sodium methoxide gave only unreacted starting material. In view of the fact that 3-acylisocoumaranones may be converted by acid into 2-substituted-3-benzofurancarboxylic acids[1,9] and since the analogous conversions have been accomplished in other heterocycles,[10] XXIX also was treated with hydrochloric acid in ethanol and in aqueous ethanol. In both cases, the only product obtained was 1-phenyloxindole (II), the benzoyl group being cleaved before ring-opening and reclosure to the indole XXXII or XXXIII could occur. This facile cleavage had been encountered previously when XXI was treated with acid, so the results with XXIX were not surprising.[11]

The ultraviolet spectrum of the by-product from XIV showed that this compound is an indole analogous to XXXI. However, the material was not the expected diester, but instead a mono-carboxylic acid resulting from saponification of one of the carbomethoxy groups. Since XXVIII gave an ester rather than the acid XXXIII, it would appear that the indole's ester group does not saponify during the reaction conditions and the by-product from XIV would be XXXIV. However, XXXI absorbs at 5.93 μ in the infrared, while the ester band in the by-product from XIV occurs at 5.80 μ. Therefore, we believe that the by-product is the alternate ester XXXV. The by-product from XV is completely analogous and is therefore the corresponding ethyl ester XXXVI.

XXXIV, R = CH₃, R′ = H
XXXV R = H, R′ = CH₃
XXXVI R = H, R′ = C₂H₅

Experimental[12]

Methyl o-Benzamidophenylacetate (VIII).—Methyl o-nitrophenylacetate,[13] prepared in 95% yield from the acid and methanolic HCl, was hydrogenated in methanol with a platinum catalyst. The solvent was then removed at room temperature to leave crude methyl o-aminophenylacetate as an orange oil. This compound previously had been prepared by Neber by esterification of o-aminophenylacetic acid.[6] The conversion into VIII was then carried out with benzoyl chloride in pyridine, in 72–78% yields based on nitroester, according to Neber's directions.[6]

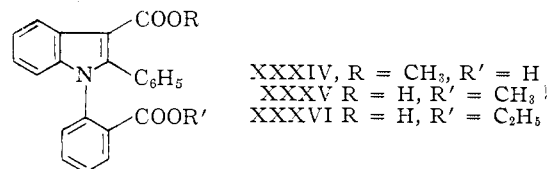**Ethyl o-Benzamidophenylacetate (IX).**—Ethyl o-nitrophenylacetate[14] was hydrogenated with platinum in absolute

(7) Recently, acyl derivatives of o-aminophenylacetic acid have been converted into 2-substituted indoles by dry distillation from soda-lime, presumably by a similar mechanism followed by decarboxylation of the resulting 3-indolecarboxylic acid; I. Murakoshi, *J. Pharm. Soc. Japan*, **79**, 72 (1959).

(8) Ethyl 1-methyl-2-phenyl-3-indolecarboxylate and the corresponding acid have been similarly prepared: W. Borsche and A. Klein, *Ann.* **548**, 64 (1941).

(9) J. N. Chatterjea, *J. Indian Chem. Soc.*, **34**, 299 (1957).

(10) F. Korte and K. H. Büchel, *Angew. Chem.*, **71**, 709 (1959).

(11) The conversion of oximes of 3-acyloxindoles into 2-substituted indoles has been carried out by E. Wenkert, B. S. Bernstein and J. H. Udelhofen, *J. Am. Chem. Soc.*, **80**, 4899 (1958). These authors, however, were unable to convert 3-acetyloxindole itself into the corresponding indole.

(12) Analyses were carried out under the supervision of Mr. M. E. Auerbach and Mr. K. D. Fleischer. Spectra were run under Dr. F. C. Nachod's supervision, ultraviolet spectra being determined in 95% ethanol and infrared spectra in potassium bromide unless otherwise stated.

(13) C. Goldschmidt, *Chem. Zeit.*, **25**, 793 (1901).

(14) A. Reissert and J. Scherk, *Ber.*, **31**, 395 (1898).

ethanol and the product converted into IX with benzoyl chloride and pyridine[6] or aqueous sodium hydroxide.

N-[o-(Carbomethoxymethyl)-phenyl]-benzimino-o-Carbomethoxyphenyl Ether (XII).—When 56.5 g. (0.21 mole) of methyl o-benzamidophenylacetate and 43.7 g. (0.21 mole) of phosphorus pentachloride were mixed, a spontaneous reaction soon occurred. The reaction was completed by heating on the steam-bath until hydrogen chloride evolution had ceased. The phosphorus oxychloride which had formed was then removed *in vacuo* at up to 50° and the last traces were removed by codistillation with toluene. This left the chloride X as a red oil.

A solution of 12.4 g. (0.23 mole) of sodium methoxide and 200 ml. of methanol was flushed with nitrogen and cooled with an ice-bath. Methyl salicylate (35.0 g., 0.23 mole) in 50 ml. of methanol was then added quickly with stirring. A solution of the above chloride X in 65 ml. of absolute ether next was added over 5 minutes and the mixture was stirred for 3 hours at room temperature. Water was added and the product extracted into ether. The red organic solution was dried and the solvent removed to leave an oil which was crystallized from methanol–hexane. Yellow prisms were obtained, m.p. 60–64°, yield 59.2 g. (70%). Two recrystallizations from methanol gave the white analytical sample, m.p. 62–65°. The ultraviolet spectrum showed λ_{max} 228 mμ, ϵ 24,000, and 278 mμ, ϵ 5,400. Infrared bands were present at 5.80 and 5.97 μ.

Anal. Calcd. for $C_{24}H_{21}NO_5$: C, 71.45; H, 5.25; O, 19.83. Found: C, 71.16; H, 5.40; O, 19.80.

N-[o-(Carbethoxymethyl)-phenyl]-benzimino o-Carbomethoxyphenyl Ether (XIII).—The chloride XI was formed, as above, from 51 g. (0.18 mole) of ethyl o-benzamidophenylacetate and 37.5 g. (0.18 mole) of phosphorus pentachloride. The imino-ether was then synthesized from 10.8 g. (0.20 mole) of sodium methoxide in 200 ml. of methanol, 30.4 g. (0.20 mole) of methyl salicylate in 50 ml. of methanol and XI in 50 ml. of anhydrous ether. The reaction and the workup were carried out as in the preparation of XII, above, the resulting crude oil being crystallized from absolute ethanol to give 47.2 g. (63%) of yellow crystals, m.p. 91–94°; ultraviolet spectrum λ_{max} 225 mμ, ϵ 27,600, and 278 mμ, ϵ 4,800. Infrared peaks were present at 5.82 and 5.99 μ. The analytical sample, obtained by two additional recrystallizations from absolute ethanol, had m.p. 92.5–96°.

Anal. Calcd. for $C_{25}H_{23}NO_5$: C, 71.93; H, 5.55; N, 3.36. Found: C, 71.83; H, 5.52; N, 3.34.

N-Benzoyl-o-carbomethoxy-o'-carbomethoxymethyldiphenylamine (XIV).—The imino-ether XII was heated at 280–295° for 12 minutes. The red gum which resulted was crystallized from methanol to furnish tan crystals, m.p. 115–117.5°. From 39.2 g. of XII, 32.6 g. (83%) of product was obtained. Two recrystallizations from methanol gave the white analytical sample, m.p. 115–118.5°. The ultraviolet spectrum exhibited maxima at 250 mμ, ϵ 13,070; 280 mμ, ϵ 6,910 and 300 mμ, ϵ 5,490. Carbonyl absorption occurred at 5.79 and 6.06 μ in the infrared.

Anal. Calcd. for $C_{24}H_{21}NO_5$: C, 71.45; H, 5.25; O, 19.83. Found: C, 71.67; H, 5.34; O, 19.70.

N-Benzoyl-o-carbethoxymethyl-o'-carbomethoxydiphenylamine (XV).—Pyrolysis of 27.2 g. of XIII for 12 minutes and crystallization of the product from absolute ethanol gave 24.8 g. (91%) of tan product, m.p. 113–116°. Two recrystallizations narrowed the m.p. range to 114.5–116°. The ultraviolet spectrum exhibited λ_{max} 280 mμ, ϵ 6,500, and 294 mμ, ϵ 5,500. Infrared peaks were present at 5.75, 5.81 and 6.04 μ.

Anal. Calcd. for $C_{25}H_{23}NO_5$: C, 71.93; H, 5.55; N, 3.36; O, 19.16. Found: C, 72.07; H, 5.60; N, 3.19; O, 19.20.

3-Benzoyl-1-(o-carbomethoxyphenyl)-oxindole (XX) and 1-(o-Carbomethoxyphenyl)-2-phenyl-3-indolecarboxylic Acid (XXXV).—The reaction was run with stirring in a nitrogen atmosphere, 19.0 g. (0.047 mole) of diester XIV in 125 ml. of hot benzene being treated all at once with 2.7 g. (0.050 mole) of sodium methoxide. The solid quickly dissolved and the solution was then refluxed for 1 hour with continuous removal of solvent. Dry benzene was added from time to time to prevent the volume from falling below 50 ml. The red solution then was cooled with an ice-bath

and water and excess hydrochloric acid added. The product was extracted into ether, the yellow solution dried, and the solvent removed to leave a solid which was recrystallized from methanol. An orange solid, m.p. 136–138°, yield 12.6 g. (72%), was obtained. This was the oxindole XX. In a similar run, a 64% yield of yellow crystals was obtained. The analytical sample, m.p. 135.5–137.5°, was light yellow, two additional recrystallizations from methanol having removed most of the color. The product gave a dark green color with ferric chloride and had ultraviolet maxima at 268 mμ, ϵ 12,600, and 320 mμ, ϵ 11,300. A chloroform solution showed infrared bands at 5.80, 6.07 and 6.15 μ, while the spectrum of the material in potassium bromide had peaks at 5.77, 6.10 and 6.15 μ.

Anal. Calcd. for $C_{23}H_{17}NO_4$: C, 74.38; H, 4.61; N, 3.77; O, 17.23. Found: C, 74.56; H, 4.90; N, 3.74; O, 17.10.

While the above run gave reasonably pure material after one recrystallization, a similar run in which toluene rather than benzene was used furnished material which melted over a very wide range. When it was boiled with a large volume of cyclohexane all but a very small fraction of the solid dissolved. The oxindole XX was obtained from the yellow solution while the white, insoluble material is believed to be the indole XXXV. The latter had m.p. 253–258° and gave a negative ferric chloride test. It dissolved in aqueous sodium bicarbonate and was reprecipitated on acidification. One recrystallization from methanol furnished the analytical sample, m.p. 254–260°. A poor carbon analysis was obtained, but the other analytical values were very good for the proposed formula. The ultraviolet spectrum had λ_{max} 235 mμ, ϵ 30,690, and 294 mμ, ϵ 16,550. The infrared spectrum had bands at 5.80, 5.92 and 6.05 μ, the one at 5.92 μ being weak and possibly due to an impurity such as XXXIV.

Anal. Calcd. for $C_{23}H_{17}NO_4$: C, 74.38; H, 4.61; N, 3.77; mol. wt., 371. Found: C, 75.11; H, 4.75; N, 3.77; mol. wt., 376.

3-Benzoyl-1-(o-carbethoxyphenyl)-oxindole (XXI) and 1-(o-Carbethoxyphenyl)-2-phenyl-3-indolecarboxylic Acid (XXXVI).—The reaction was run under nitrogen with stirring, 2.76 g. (0.12 g. atom) of sodium being dissolved in commercial absolute ethanol followed by distillation to dryness. The last traces of ethanol were removed by adding toluene and again distilling to dryness. A solution of 43.0 g. (0.103 mole) of diester XV in 125 ml. of dry toluene was then added all at once, a clear, red, solution soon resulting. This was refluxed for 2 hours with continuous distillation of solvent and addition of fresh, dry toluene whenever needed. The work-up was the same as for the analogous methyl ester XX, above. The crude product was recrystallized from absolute ethanol to give 29.0 g. (73%) of the oxindole XXI as a yellow solid, m.p. 134–139°. Two recrystallizations from ethyl acetate furnished the light yellow analytical sample, m.p. 142–144°. The product gave a dark green color with ferric chloride and its ultraviolet spectrum had λ_{max} 268 mμ, ϵ 14,900, and 321 mμ, ϵ 13,000. The infrared spectrum of the compound in potassium bromide had bands at 5.85, 6.06 and 6.16 μ, while a chloroform solution gave bands at 5.83, 6.07 and 6.12 μ.

Anal. Calcd. for $C_{24}H_{19}NO_4$: C, 74.79; H, 4.97; N, 3.63. Found: C, 75.44; H, 5.61; N, 3.66.

Concentration of the mother liquors from the above oxindole gave 2 g. of solid, m.p. 275–279°. Two recrystallizations from absolute ethanol gave white material, m.p. 278–281°, which gave a negative ferric chloride test and is believed to be the indole XXXVI. The ultraviolet spectrum had λ_{max} 237 mμ, ϵ 31,100, and 294 mμ, ϵ 17,340. The infrared spectrum had peaks at 5.80, 5.94 (weak) and 6.05–6.10 μ.

Anal. Calcd. for $C_{24}H_{19}NO_4$: C, 74.79; H, 4.97; N, 3.63; O, 16.61. Found: C, 74.75; H, 5.61; N, 3.61; O, 16.80.

The oxindole XXI also was prepared from the dimethyl ester XIV and sodium ethoxide in toluene. The product, m.p. 128–133°, obviously was not pure. However, that transesterification had occurred was proved by mixed melting points, that with the methyl ester XX being 118–124°, with the ethyl ester XXI 133–138°. The infrared spectrum of this material was identical with that from pre-

viously prepared XXI and different from that of the methyl ester.

o-(2-Carboxyanilino)-phenylacetic Acid (XXIII).—A solution of 16.1 g. (0.04 mole) of diester XIV, 35 g. of potassium hydroxide, 150 ml. of water and 75 ml. of dioxane was refluxed for 16 hours. The red solution was washed with ether, then acidified with excess hydrochloric acid below 15°. The gum which formed was extracted into ether and the yellow solution dried. Solvent removal left a solid which was recrystallized from ethyl acetate to give only 3.0 g. (28%) of product, m.p. 177.5–179.5° dec. In a similar run with 3 g. of XIV, a 40% yield resulted. An additional recrystallization gave the analytical sample, m.p. 181–183° dec. The ultraviolet spectrum had maxima at 220 mμ, ε 28,700; 283 mμ, ε 9,800; and 345 mμ, ε 7,100. The infrared spectrum had bands at 3.04 and 5.95 μ.

Anal. Calcd. for $C_{15}H_{13}NO_4$: C, 66.41; H, 4.83; N, 5.16; neut. equiv., 135.6. Found: C, 66.75; H, 4.76; N, 5.09; neut. equiv., 136.8.

This acid was also prepared from the cyclization product XXI, 2 g. being treated with 3 g. of potassium hydroxide in 60 ml. of water. The red solution was refluxed for 2 hours to yield, after one recrystallization from ethyl acetate, 550 mg. (38%) of acid. A second recrystallization gave white solid, m.p. 181–183° dec. A mixed melting point with the above material showed no depression and the infrared and ultraviolet spectra of the two samples proved their identity.

When 2 g. of the Chapman product XIV was refluxed for 1 hour with a solution from 3 g. of potassium hydroxide and 50 ml. of water only one of the ester groups was saponified and the amide linkage was untouched. The 1.5 g. of crude product which precipitated upon acidification of the basic solution was recrystallized from acetone–hexane to give material with m.p. 208–210° dec. The infrared spectrum, with bands at 5.78, 5.92 and 6.02 μ, suggests that the product is methyl *o*-(N-benzoyl-2-carboxyanilino)-phenylacetate, although the alternative half-ester cannot be excluded.

Anal. Calcd. for $C_{23}H_{19}NO_5$: C, 70.94; H, 4.92; N, 3.60. Found: C, 70.55; H, 4.79; N, 3.54.

1-(*o*-Carboxyphenyl)-oxindole (XXIV).—A solution of 0.8 g. of the dibasic acid XXIII, 10 ml. of acetic acid and 10 ml. of 48% hydrobromic acid was refluxed for a half-hour. On dilution with water, a solid resulted; one recrystallization from ethyl acetate gave material with m.p. 206–209°. The ultraviolet spectrum had λ_max 248 mμ, ε 11,400, while infrared peaks were present at 5.88 and 6.02 μ.

Anal. Calcd. for $C_{15}H_{11}NO_3$: C, 71.14; H, 4.37; N, 5.53. Found: C, 71.11; H, 4.80; N, 5.39.

The same acid was obtained by refluxing a solution of 6.8 g. (0.018 mole) of 3-benzoyl-1-(*o*-carbomethoxyphenyl)-oxindole (XX), 60 ml. of acetic acid and 60 ml. of 48% hydrobromic acid for 1 hour. Dilution with water gave brown crystals which were recrystallized from ethyl acetate–hexane (charcoal) to give 1.9 g. (41%) of white solid, m.p. 207.5–209.5°. This was recrystallized from ethyl acetate to yield the analytical sample having the same m.p. This product was identical, by mixed m.p. and infrared and ultraviolet spectra, with authentic XXIV prepared from dibasic acid, above.

The same compound was similarly prepared from the ethyl ester XXI.

1-(*o*-Carbethoxyphenyl)-oxindole (XXV).—A solution of 4.9 g. (0.013 mole) of XXI, 40 ml. of ethanol, 30 ml. of concd. HCl and 20 ml. of dioxane was refluxed for 12 hours. Water was added and the mixture extracted with ether. The extracts were washed with aqueous sodium bicarbonate, then dried and the solvent removed to give a gum which was crystallized from hexane. Only 1.2 g. (32%) of light brown solid, m.p. 115–119°, was obtained; undoubtedly, higher yields could be obtained by running the reaction under anhydrous conditions. Two recrystallizations from isopropyl alcohol raised the m.p. to 118.5–121.5°. Ultraviolet maxima were present at 228 mμ, ε 14,270; 246 mμ, ε 12,030; and 280 mμ, ε 2,210. The infrared spectrum showed only one carbonyl band, at 5.82 μ.

Anal. Calcd. for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 73.04; H, 5.21; N, 4.70.

3-Benzoyl-1-(*o*-carboxyphenyl)-oxindole (XXII).—An attempt to hydrolyze the cyclization product XX with

potassium bicarbonate in aqueous methanol had failed, unreacted starting material being recovered; therefore, a stronger base was used. A solution of 10.0 g. (0.027 mole) of XX, 20 g. of potassium carbonate, 500 ml. of methanol and 125 ml. of water was refluxed for 3 hours, then diluted with water and washed with ether. The aqueous phase was acidified with HCl and the product extracted into ether. Drying and solvent removal yielded a red oil which was crystallized from benzene–hexane to give 6.3 g. (66%) of solid, m.p. 203–207.5°. One recrystallization from benzene furnished the analytical sample as a light yellow solid, m.p. 206–209°. The product gave a green color with ferric chloride and was soluble in aqueous bicarbonate. The ultraviolet spectrum had λ_max 270 mμ, ε 11,400, and 321 mμ, ε 11,030. The infrared spectrum had bands at 5.96, 6.09 and 6.12 μ.

Anal. Calcd. for $C_{22}H_{15}NO_4$: C, 73.94; H, 4.23; N, 3.92; neut. equiv., 178.7. Found: C, 74.01; H, 4.44; N, 3.91; neut. equiv., 183.0.

When a portion of XXII was heated no carbon dioxide evolution occurred even at 360°. When 360 mg. of XXV in 2 ml. of sulfuric acid was heated to 250°, no carbon dioxide was evolved.

The Cyclization of Methyl *o*-(N-Benzoylanilino)-phenylacetate (XXVIII) to XXIX and XXXI.—The reaction was run as above for the cyclization of XIV, 1.38 g. (4 mmoles) of XXVIII[1] and 270 mg. (5 mmoles) of sodium methoxide being used. After dilution with water, the mixture was extracted with chloroform to give the neutral fraction. The aqueous solution was acidified and extracted with chloroform, drying and solvent removal then furnishing a gum. This was crystallized from isopropyl alcohol to yield 420 mg. (34%) of 3-benzoyl-1-phenyloxindole (XXIX) as a tan solid, m.p. 118–121°. There was no melting point depression when mixed with authentic XXIX (below). The infrared spectrum showed poorly resolved bands at 6.05, 6.10 and 6.15 μ, identical with the spectrum of the authentic material. The ultraviolet spectrum had λ_max 229 mμ, ε 21,600; 271 mμ, ε 11,500; and 323 mμ, ε 10,100. The product gave an intense color with ferric chloride. One recrystallization from cyclohexane did not change the melting point.

Anal. Calcd. for $C_{21}H_{15}NO_2$: N, 4.47. Found: N, 4.21.

The neutral material was crystallized from methanol (charcoal) to give 90 mg. (7%) of crude methyl 1,2-diphenyl-3-indolecarboxylate (XXXI), m.p. 170–189°. An additional recrystallization from the same solvent furnished white needles, m.p. 193.5–195°. The substance did not depress the melting point of the authentic material (below). The infrared spectrum was very similar to that of the authentic sample, but contained a few, weak, additional peaks, including one at 5.87 μ. It is possible that these bands were due to 1-phenyloxindole, a likely contaminant. The product gave no color with ferric chloride and had ultraviolet maxima at 235 mμ, ε 29,100, and 294 mμ, ε 17,100.

Anal. Calcd. for $C_{22}H_{17}NO_2$: C, 80.71; H, 5.23; N, 4.28. Found: C, 80.46; H, 5.16; N, 4.10.

3-Benzoyl-1-phenyloxindole (XXIX).—A sodium ethoxide solution was prepared from 2.3 g. of sodium and 40 ml. of absolute ethanol. To this was added quickly a warm solution of 8.4 g. (0.04 mole) of 1-phenyloxindole,[15] 50 ml. of ethanol and 15 g. (0.1 mole) of ethyl benzoate. The mixture was refluxed for 2 hours, considerable solid precipitating. After cooling and diluting with water, neutral material was removed by ether extraction and unreacted 1-phenyloxindole was recovered. (In one run, the reaction mixture was refluxed for 18 hours to furnish a different, unknown, neutral material, m.p. 175–180°. The yield of XXIX was very low.) The aqueous solution then was acidified with HCl and extracted with ether. Drying, solvent removal, and recrystallization from ethanol–cyclohexane furnished 2.3 g. (18%) of yellow solid, m.p. 107–114°. Two recrystallizations from isopropyl alcohol gave material, m.p. 117.5–120.5°, which was identical with that from XXVIII.

Anal. Calcd. for $C_{21}H_{15}NO_2$: C, 80.49; H, 4.83; N, 4.47. Found: C, 80.82; H, 4.66; N, 4.45.

Ethyl 1,2-Diphenyl-3-indolecarboxylate (XXXII).—N,N-Diphenylhydrazine and ethyl benzoylacetate were

(15) R. Stollé, *Ber.*, **47**, 2120 (1914).

converted into the hydrazone[16] XXX and 39 g. (0.11 mole) of this material was dissolved in 250 ml. of warm absolute ethanol. To this was added 250 ml. of ethanol saturated with HCl. The red solution, on boiling for 1 hour, turned yellow and a precipitate formed. On dilution with water, the product was obtained as an insoluble, yellow solid. One recrystallization from ethanol gave white product, m.p. 149–150.5°, 17.5 g. (47%) being obtained. The ultraviolet spectrum had λ_{max} 235 mμ, ϵ 30,000, and 294 mμ, ϵ 17,600. The carbonyl absorption occurred at 5.92 μ in the infrared.

Anal. Calcd. for $C_{23}H_{19}NO_2$: C, 80.91; H, 5.61; N, 4.10. Found: C, 81.03; H, 5.64; N, 4.09.

1,2-Diphenyl-3-indolecarboxylic Acid (XXXIII).—A mixture of 3 g. of ethyl ester XXXII, 25 ml. of 35% aqueous sodium hydroxide, 15 ml. of water and 50 ml. of methanol was refluxed for 18 hours. The mixture then was cooled and solid filtered; this was the sodium salt of the product. When dissolved in hot water and treated with excess hydrochloric acid, this furnished XXXIII as a white solid. The analytical sample was obtained by recrystallizing twice from acetone to give material with m.p. 244–245° dec. Ultraviolet maxima occurred at 234 mμ, ϵ 29,000, and 294 mμ, ϵ 16,800. The infrared spectrum had a band at 6.05 μ.

Anal. Calcd. for $C_{21}H_{15}NO_2$: C, 80.49; H, 4.83; N, 4.47. Found: C, 80.42; H, 4.67; N, 4.40.

A portion of the sodium salt was recrystallized from water to give white needles, m.p. > 300°.

Anal. Calcd. for $C_{21}H_{14}NO_2Na$: C, 75.21; H, 4.21; N, 4.18. Found: C, 75.26; H, 4.34; N, 3.99.

In a similar run with 10.2 g. (0.03 mole) of ester, 6.5 g. (69%) of acid was obtained.

(16) A. Hantzsch and E. v. Hornbostel, *Ber.*, **30**, 3009 (1897).

Methyl 1,2-Diphenyl-3-indolecarboxylate (XXXI).—Since an attempt to prepare this compound by transesterification of XXXII with sodium methoxide in methanol gave only a very impure product, the route *via* the acid chloride was chosen. This was prepared from 1 g. of acid XXXIII and 10 ml. of thionyl chloride, the solution being refluxed for 45 minutes after the initial reaction had stopped. The excess reagent was then removed *in vacuo*, 10 ml. of methanol added, and the mixture refluxed for 45 minutes. After cooling, the insoluble product was separated and recrystallized from methanol (charcoal) to yield white needles, m.p. 195–196°. The product was essentially the same as the by-product from the cyclization of XXVIII, above. The carbonyl group absorbed at 5.93 μ in the infrared. The ultraviolet spectrum had λ_{max} 235 mμ, ϵ 29,800, and 294 mμ, ϵ 17,600.

Anal. Calcd. for $C_{22}H_{17}NO_2$: C, 80.71; H, 5.23; N, 4.28. Found: C, 80.67; H, 5.01; N, 4.25.

Attempted Conversions of XXIX into Indoles.—A mixture of 1 g. of XXIX, 1 g. of sodium methoxide and 15 ml. of dry xylene was refluxed for 5 hours. Only a trace of neutral material resulted. The acidic fraction yielded unreacted XXIX.

A solution of 0.8 g. of XXIX and 20 ml. of ethanolic HCl was refluxed for 3 hours to give a light red solution which gave a negative ferric chloride test. On dilution with water a tan solid resulted. This, on recrystallization from 95% ethanol, furnished a white solid, m.p. 121–123°, mixed m.p. with 1-phenyloxindole[15] 122–123.5°. Since the hoped-for indoles XXXII or XXXIII are less soluble than 1-phenyloxindole, little or any could have been formed.

When a solution of 0.5 g. of XXIX, 30 ml. of ethanol, 10 ml. of concentrated aqueous HCl and 10 ml. of water was refluxed for 5 hours, 1-phenyloxindole was again the only product isolated.

The Chemistry of Fumagillin[1]

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Experimental evidence is presented and discussed which allows the assignment of structures to fumagillin and its transformation products.

The chemistry of fumagillin has been intensively investigated[3–11] since its isolation.[12] Its antiparasitic properties[13] and its carcinolytic activity against some experimental tumors[14] have stimulated studies of the biological properties of compounds in this series.

Fumagillin was early[3,4] shown to be an acid ester, yielding on mild saponification decatetraenedioic acid, and a neutral fragment, $C_{16}H_{26}O_4$, called[15] alcohol-I. The present paper discusses the experimental evidence, mainly published only in preliminary form,[11,16,17] which allows the assign-

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(2) (a) Abbott Laboratories Fellow, 1960–1961; (b) 1957–1958; (c) Esso Fellow, 1960–1961; (d) Abbott Laboratories Fellow, 1959–1960; (e) 1956–1957; (f) 1958–1959.

(3) J. R. Schenck, M. P. Hargie, D. S. Tarbell and P. Hoffman, *J. Am. Chem. Soc.*, **75**, 2274 (1953).

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(5) D. S. Tarbell, P. Hoffman, H. R. Al-Kazimi, G. A. Page, J. M. Ross, H. R. Vogt and B. Wargotz, *ibid.*, **77**, 5610 (1955).

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(7) J. K. Landquist, *J. Chem. Soc.*, 4237 (1956).

(8) J. G. McNally, Jr., and D. S. Tarbell, *J. Am. Chem. Soc.*, **80**, 3676 (1958).

(9) D. D. Chapman and D. S. Tarbell, *ibid.*, **80**, 3679 (1958).

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(12) T. E. Eble and F. R. Hanson, *Antibiotics and Chemotherapy*, **1**, 54 (1951); *cf.* I. N. Asheshov, F. Strelitz and E. A. Hall, *ibid.*, **2**, 361 (1952).

(13) (a) Amoebacidal activity: M. C. McCowen, M. E. Callender and J. F. Lawlis, Jr., *Science*, **113**, 202 (1951); H. H. Anderson, *et al.*,

Am. J. Trop. Med. Hyg., **1**, 552 (1952); J. H. Killough, G. B. Magill and R. C. Smith, *Science*, **115**, 71 (1952); (b) activity against *Nosema apis*, H. Katznelson and C. A. Jamieson, *ibid.*, **115**, 70 (1952).

(14) J. A. DiPaolo, D. S. Tarbell and G. E. Moore, *Antibiotics Annual*, 1958–1959, p. 541.

(15) The systematic nomenclature for these compounds is so cumbersome—alcohol-I has been called oxiranspiro-[2-(3-isopent-2'-enyl-1'-methoxyloxiranyl)-3-methoxycyclohexan-4-ol] (*Current Chem. Papers*, 290 (1960))—that some trivial nomenclature is necessary. The use of a name such as fumagillane for the parent hydrocarbon, with the indication of the oxygen functions by numbers, has little to recommend it. The use of "fumagillol"[7] for alcohol-I requires special indications for the diols and triols obtained by reductive opening of the epoxide groups. We have therefore retained the trivial names used in earlier papers of this series, when the complete structures were not known, in order to show the structures of the compounds discussed in the earlier papers. The suffix "a" refers to reduction of the side chain double bond, and "b" to the reductive opening of the spiroepoxide.