Limitations in Ring Rearrangement of Fused γ-Lactams Imposed by a Quaternary Carbon Atom. Cyclization of Acid Lactams to Spiro Keto Lactams

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Through spectra, derivatives, and cyclizations to spirooxindoleindanones and spirooxindoletetralones, it is demonstrated that 1,3-disubstituted oxindole-3-acetic acids do not rearrange to 4-carboxyhydrocarbostyrils. Ring contractions, revolving around a quaternary carbon atom, of 2,3,4,5-tetrahydro-6,7-benzazepin-2-one-5-carboxylic acids and related seven-membered lactams take place as previously reported for simpler analogs.

In the study of comparative stability of oxindoles, carbostyrils, and benzazepinones, early erroneous reports of synthesis of isatylideneacetic, oxindole-3-glyoxylic, and oxindole-3-acetic acids by routes involving hydrolysis of corresponding esters[1–3] were corrected when it was shown that these rearrange hydrolytically to 4-carboxycarbostyrils or hydrocarbostyrils.[4–8] The knowledge of lactam ring rearrangements was broadened when it was shown that 5-carboxy-2,3,4,5-tetrahydro-6,7-benzazepin-2-ones rearrange solvolytically into oxindole-3-propionic acids,[9] and that 4-carboxy-2,3,4,5-tetrahydro-6,7-benzazepin-2-ones rearrange similarly to 3-carboxymethyl-3,4-dihydrocarbostryrils.[10] More evidence to support the preferred formation of hydrocarbostyrils[11,12] and oxindoles[11] in place of seven-membered lactams was found in other solvolytic rearrangements and in reduction of appropriate nitro compounds. It is now clear, however, that any generalization (six > five > seven) in regard to relative stability of various-sized, simple fused ring lactams which might have been drawn from this work applies only to cyclic reactions of carboxyl groups with aniline nitrogen, and is not to be extended to competitions between carboxyl and carbonyl groups, because it has been shown recently that 4-acyl-3,4-dihydro-2-quinolones rearrange solvolytically to indole-3-acetic acid derivatives.[13]

An interest in learning how these principles might apply to lactam ring rearrangements in more highly substituted systems stimulated the present work. One purpose of this paper is to show that, in tetrahydrobenzazepin-2-one-5-carboxylic and -5-acetic acids, lactam rearrangement holds true to type,[9,10] even when it involves changes centered at a quaternary carbon atom, but that, in oxindole-3-acetic acids having a quaternary 3-carbon atom, the older, and heretofore even better established, change from oxindole to six-membered lactam does not take place. The latter conclusion was foreshadowed by recently observed nonrearrangement of 3-quaternary oxindoles carrying other 3-groups potentially capable of reacting with aniline nitrogen.[14]

One phase of the work began with alkylation of a number of 1-substituted 3-aryl- and 3-benzyloxindoles (I, III, and V, see Scheme I), which are described in another paper.[15] Chloroacetonitrile[16–18] alkylation of I and of Va and e in the presence of sodium methoxide gave IIc and VIIa and e, respectively. Compound I also reacted rapidly with allyl bromide under the same conditions, giving IIe, an oil which was characterized through bromination to give a crystalline dibromide. The dibromide was not found to be prone to ring changes when treated with various bases.[14] Alkylation of I with bromoacetal was difficult, giving poor results with sodium methoxide and somewhat better results when sodamide was used. In contrast with results in bromoacetal alkylation of 1,3-dimethyloxindoles,[19] a by-product, 1-methyl-3-phenyldioxindole, was formed, possibly arising through alkaline air oxidation of I, but not observed in alkylations using other halides.[20] The other product, acetal IId, was not crystalline, but was characterized by acid hydrolysis to the corresponding oxindole-3-acetaldehyde.[19] Next examined were alkylations of I, III, and V with ethyl bromoacetate. These reactions proceeded readily in the presence of methanolic sodium methoxide and were accompanied by ester exchange, giving IIb, IV, and VI. The ester exchange, clearly a complete one in preparation of compounds IIb, IVa, and VIa, and observed less precisely in reactions leading to other crystalline esters, IVb and VIb, may argue in favor of ring–chain tautomeric interaction between newly introduced acetic ester group and oxindole carbonyl, leading in the end to formation of ester corresponding to the alcohol present in excess. This is reasonable in the light of tetrahedral 2-carbon, 3-quaternary oxindoles, reported in other studies,[14] and indicates that electronic opportunity is not lacking in these cases for solvolytic ring rearrangement to occur, but evidently the steric environment

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[9] H. A. Lloyd and E. C. Horning, *ibid.*, **76**, 3651 (1954).

[10] H. A. Lloyd, L. U. Matternas, and E. C. Horning, *ibid.*, **77**, 5932 (1955).

[11] G. N. Walker, *ibid.*, **78**, 3698 (1956).

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[13] E. Ochai, H. Kataoka, T. Dodo, and M. Takahashi, *Chem. Pharm. Bull. Japan*, **10**, 76 (1962); E. Ochai, M. Takahashi, Y. Tamai, and K. Kataoka, *ibid.*, **11**, 137 (1963).

[14] H. E. Zaugg and R. W. De Net, *J. Am. Chem. Soc.*, **84**, 4574 (1962).

[15] G. N. Walker, R. T. Smith, and B. N. Weaver, *J. Med. Chem.*, **8**, 626 (1965).

[16] P. L. Julian, J. Pikl, and D. Boggess, *J. Am. Chem. Soc.*, **56**, 1797 (1934).

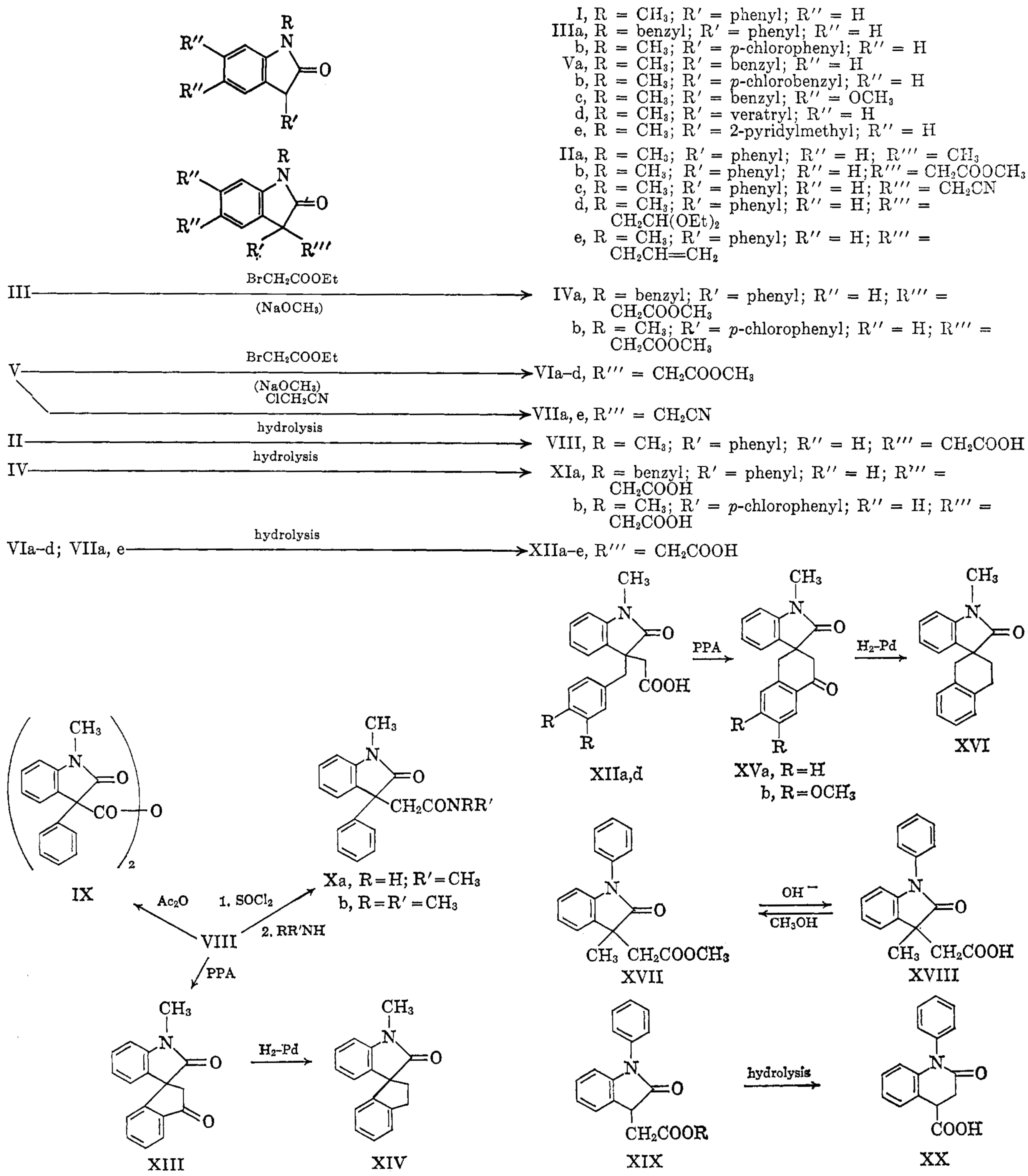
[17] P. L. Julian and J. Pikl, *ibid.*, **57**, 755 (1935).

[18] E. C. Horning and M. W. Rutenberg, *ibid.*, **72**, 3534 (1950).

[19] P. L. Julian, J. Pikl, and F. E. Wantz, *ibid.*, **57**, 2026 (1935).

[20] An alternative route to formation of this dioxindole may possibly be through attack of hypobromite formed by an abnormal breakdown of bromoacetal. The ease of hypohalite oxidation of oxindole-3-alanines and -3-propionic acids has been noted previously: see P. L. Julian, H. C. Printy, and E. E. Dailey, *ibid.*, **78**, 3501 (1956); P. L. Julian, E. E. Dailey, H. C. Printy, H. L. Cohen, and S. Hamashige, *ibid.*, **78**, 3503 (1956).

SCHEME I



I, R = CH_3; R′ = phenyl; R″ = H
IIIa, R = benzyl; R′ = phenyl; R″ = H
b, R = CH_3; R′ = *p*-chlorophenyl; R″ = H
Va, R = CH_3; R′ = benzyl; R″ = H
b, R = CH_3; R′ = *p*-chlorobenzyl; R″ = H
c, R = CH_3; R′ = benzyl; R″ = OCH_3
d, R = CH_3; R′ = veratryl; R″ = H
e, R = CH_3; R′ = 2-pyridylmethyl; R″ = H

IIa, R = CH_3; R′ = phenyl; R″ = H; R‴ = CH_3
b, R = CH_3; R′ = phenyl; R″ = H; R‴ = CH_2COOCH_3
c, R = CH_3; R′ = phenyl; R″ = H; R‴ = CH_2CN
d, R = CH_3; R′ = phenyl; R″ = H; R‴ = $CH_2CH(OEt)_2$
e, R = CH_3; R′ = phenyl; R″ = H; R‴ = $CH_2CH{=}CH_2$

III $\xrightarrow[(NaOCH_3)]{BrCH_2COOEt}$ IVa, R = benzyl; R′ = phenyl; R″ = H; R‴ = CH_2COOCH_3
b, R = CH_3; R′ = *p*-chlorophenyl; R″ = H; R‴ = CH_2COOCH_3

V $\xrightarrow[(NaOCH_3)]{BrCH_2COOEt}$ VIa–d, R‴ = CH_2COOCH_3

V $\xrightarrow{ClCH_2CN}$ VIIa, e, R‴ = CH_2CN

II $\xrightarrow{hydrolysis}$ VIII, R = CH_3; R′ = phenyl; R″ = H; R‴ = CH_2COOH

IV $\xrightarrow{hydrolysis}$ XIa, R = benzyl; R′ = phenyl; R″ = H; R‴ = CH_2COOH
b, R = CH_3; R′ = *p*-chlorophenyl; R″ = H; R‴ = CH_2COOH

VIa–d; VIIa, e $\xrightarrow{hydrolysis}$ XIIa–e, R‴ = CH_2COOH

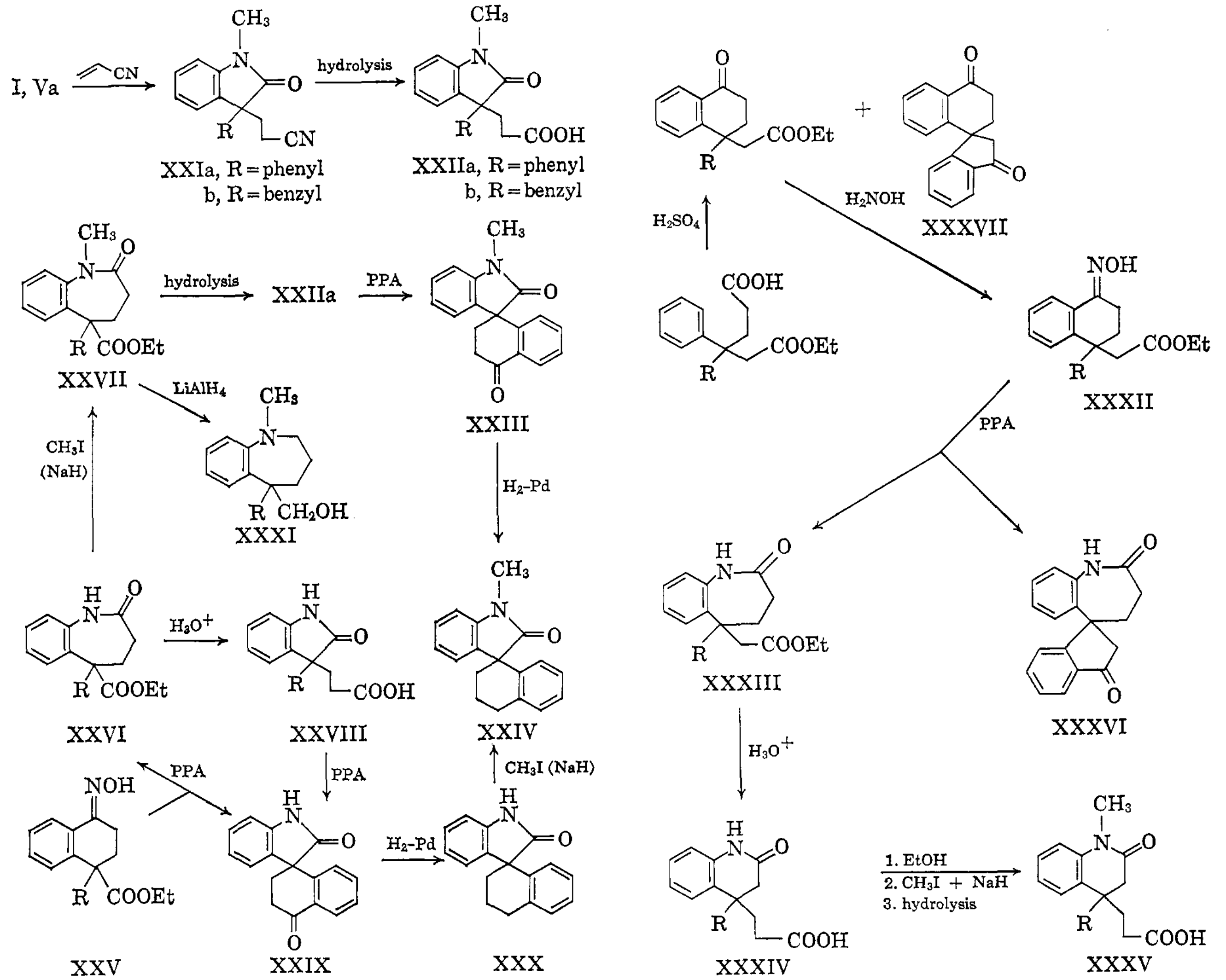
Xa, R = H; R′ = CH_3
b, R = R′ = CH_3

XVa, R = H
b, R = OCH_3

of the oxindole carbonyl group prevents it. The spectra of IIb, IVa, b, and VIa–c, with infrared oxindole bands (5.81–5.86 μ), indicated that no rearrangement had occurred. This became clearer when nitrile IIc and ester IIb were hydrolyzed. The product, acid VIII, also had an intact infrared oxindole peak, as did also derived anhydride IX and two amides X, and esterification of VIII with methanol[9,10] gave back IIb. Hydrolysis of other 3-aryloxindole-3-acetic esters IV was also found to proceed without rearrangement, to give acids XI, the spectra of which were in keeping with that of VIII.

When 3-benzyloxindoleacetic esters VI and nitrile VIIa were hydrolyzed, crystalline acids XII were obtained uniformly, even from the more poorly characterized, crude esters VIc, d, and e. The solid-state infrared spectra of acids XIIa–d had strong bands 5.95–6.0 μ as well as peaks at 5.70–5.75 μ. These initially misleading peaks at *ca.* 6.0 μ did not, however, prove to be owing to carbonyl groups of six-membered lactams. Re-esterification of XIIa returned VIa, and an additional way was found to prove the structures of compounds such as VIII and XII. Spirocyclization of VIII with polyphosphoric acid gave neutral

Scheme II[a]



[a] Unless otherwise indicated, R = phenyl.

product XIII, the infrared spectrum of which had a close oxindole–indanone doublet 5.82–5.90 μ. Similar spirocyclizations of XIIa and XIId gave, respectively, ketones XVa and XVb, showing infrared oxindole–tetralone (5.84–5.89 and 5.95–5.97 μ) doublets. Ultraviolet spectra of indanone XIII and tetralones XV were also consonant with the development of the new, conjugated ketone function. Hydrogenolysis of the spiro ketones in acetic acid (palladium) converted XIII to XIV, and XVa to XVIa, resulting in disappearance of the infrared and ultraviolet aryl ketone absorption and return to characteristic oxindole spectra.

Additional evidence proving that oxindole-3-acetic acids with quaternary 3-carbon atoms do not rearrange to hydrocarbostyrils was obtained by investigation of N-phenyloxindole-derived compounds. Alkylation of 1-phenyl-3-methyloxindole[15] with ethyl bromoacetate provided ester XVII, and subsequent hydrolysis gave unrearranged acid XVIII. In contrast, esters XIX of 1-phenyloxindole-3-acetic acid, reliably prepared by hydrogenolysis of N-phenyloxindole-3-glyoxylates, upon hydrolysis rearranged to acid XX, having spectra consistent with the N-aryldihydrocarbostyril structure, as did also its corresponding methyl ester.

It is evident that differences in degree or kind of substitution on the aniline nitrogen make no difference in the question of ring rearrangement or the lack of it in oxindole-3-acetic acids, but that the latter is governed by the degree of substitution on the 3-carbon. Moreover it is immaterial what the size may be of the additional 3-substituent which prevents rearrangement of an oxindole-3-acetic acid to a hydrocarbostyril. It follows that the structure of 1,3-dimethyloxindole-3-acetic acid as originally reported by Julian, Pikl, and Boggess[16] must after all be correct, later assertions[7,21] that the structure should be revised to 1,4-dimethyl-3,4-dihydro-2-quinolone-4-carboxylic acid being in error.

Attention was directed next to oxindole-3-propionic acids, and 3-phenyl-substituted examples of this type were prepared by two converging routes (see Scheme II). Cyanoethylation[18] of I and Va gave nitriles XXIa and XXIb, respectively. Acid XXIIa, from hydrolysis of XXIa, was spirocyclized with polyphosphoric acid to ketone XXIII (infrared 5.95 μ, tetralone), and again palladium hydrogenolysis of the tetralone resulted in product XXIV, spectrally devoid of all but the N-methyloxindole group. With these compounds on hand one could resolve clearly the question of whether hydrobenzazepinone XXVI and relatives, with the

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[21] W. C. Sumpter, *Chem. Rev.*, **37**, 443 (1945).

carboxylic group attached directly to the quaternary carbon, would undergo rearrangement. Compound XXVI was obtained by polyphosphoric acid promoted Beckmann rearrangement[9,10,22] of XXV, the oxime of now known 4-carboxy-4-phenyl-1-tetralone.[23] Reaction of XXV with polyphosphoric acid gave not only predicted XXVI with expected infrared (ester 5.77 μ, lactam 5.96 μ) bands, but also a by-product. The latter, with infrared oxindole (5.85 μ) and conjugated ketone (5.92 μ) peaks, ultraviolet spectrum indicating a benzoyl group, and analysis showing loss of an oxygen atom, was believed to be spiro ketone XXIX. Since in this case spirocyclization is possible only *after* ring rearrangement, evidence was already at hand indicating facile rearrangement of XXVI. Deliberate hydrolytic rearrangement of XXVI then gave, as expected, acid XXVIII which showed an infrared oxindole peak, as did also its corresponding methyl ester. Subsequent polyphosphoric acid spirocyclization of XXVIII gave XXIX, identical with that which had been obtained as by-product in the Beckmann expansion. N-Methylation of XXVI gave XXVII, again showing infrared ester (5.78 μ) and lactam (6.00 μ) maxima. Upon being subjected to hydrolytic ring rearrangement, XXVII now led to oxindole propionic acid XXIIa, identical with that obtained from cyanoethylated N-methyloxindole XXIa. Completing the relationships which had been established, it was also demonstrated that spiro compound XXIX, upon hydrogenolysis to XXX and subsequent N-methylation, gave spirooxindole XXIV, identical with that resulting from hydrogenolysis of XXIII. In addition, lactam XXVII was reduced with lithium aluminum hydride to amino alcohol XXXI, spectrally devoid of carbonyl chromophores.

Beckmann expansion of XXXII[23] with polyphosphoric acid also was carried out. The major product, probably XXXIII, could not be made to crystallize, although a crystalline by-product was isolated in small quantity. To the latter, structure XXXVI is assigned, because the infrared spectrum had 5.78- and 5.98-μ peaks, respectively indicating indanone and seven-membered lactam groups (rather than tetralone and hydrocarbostyril), and analysis and ultraviolet spectrum also indicated spiro ketone closure. In respect to the indanone band, the spectrum of XXXVI agrees with both that of XIII (5.82 μ) and with that of compound XXXVII (5.85–5.87 μ) which is obtained readily[23] from the parent tetralone.

When crude XXXIII was hydrolyzed, the rearranged dihydrocarbostyrilpropionic acid XXXIV was obtained in rather low yield (*ca.* 10%). The infrared spectrum of XXXIV, with carboxyl (5.86 μ) and lactam (6.05 μ) peaks, could not be relied upon alone to distinguish between six- and seven-membered rings, although the lactam value was closer to that anticipated for the former, as is evident when it is compared with that of XXVI. Therefore, first protecting the acid group of XXXIV as ester, the compound was methylated, and, after rehydrolysis, the corresponding N-methyl lactam acid XXXV also was examined spectrally. The lactam peak now was seen at 6.13 μ in the infrared which, when contrasted with the value for XXVII, made it clearer that a dihydrocarbostyril was present. Further evidence for this was provided by the ultraviolet curve of XXXV [λ_{max} 254 mμ (ϵ 10,460)] which was quite different from that of XXVII or XXVI [λ_{max} *ca.* 230 mμ (ϵ *ca.* 11,000)] because of the greater aryl–N resonance in the six-membered ring. Spirocyclizations of XXXIV or XXXV were tried in an effort to provide further evidence for the structures, but limited quantities of material and the fact that these exploratory attempts gave very poor results, precluded further work. The neutral, impure products of these reactions, obtained in very low yield, at least did not show infrared carbonyl absorption near 5.8 μ, as they would have if indanone rings had formed.

Experimental[24]

Methyl 1-Methyl-3-phenyloxindole-3-acetate (IIb).—To a solution of 1.3 g. (0.0565 g.-atom) of sodium in *ca.* 150 ml. of methanol were added 10 g. (0.045 mole) of 1-methyl-3-phenyloxindole[25] and then 10 ml. (15.1 g., 0.09 mole) of ethyl bromoacetate. The solution was refluxed 4.5 hr., then evaporated to smaller volume on the steam cone. The cooled residue was treated with water, which then showed a neutral pH. An oil separated and crystallized when rubbed. The product was collected, washed with several portions of water, air dried, and triturated with a small quantity of ether to remove oily material. The yield of colorless crystals, m.p. *ca.* 85–88°, was 8.2 g. (62%). A pure sample, prepared by recrystallization from ether, had m.p. 91.5–93°; λ_{max} 5.75, 5.84, and 6.18 μ in chloroform; λ_{max}^{Nujol} 5.74, 5.85, and 6.20 μ; and λ_{max}^{EtOH} 256 mμ (ϵ 7650) with an inflection at 286 mμ (ϵ 1530).

Anal. Calcd. for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 72.91; H, 5.62; N, 4.80.

A polymorphic form of the methyl ester was obtained in another experiment in which the crude product, after treatment with water, was not allowed to crystallize in the presence of base but was extracted immediately with ether, and the ether solution, after washing to neutrality and drying, was evaporated. Trituration with ether gave colorless crystals: m.p. 95–96°, λ_{max}^{Nujol} 5.75, 5.81, and 6.18 μ, and not identical in the fingerprint region with spectrum of the m.p. 91.5–93° form; $\lambda_{max}^{CHCl_3}$ identical with the first sample. The same higher melting form was obtained, as described below, by methanol esterification of the corresponding acid. When recrystallized from ether or other solvents, the m.p. 95–96° form reverted to the lower melting form, and the mixture melting point of the two forms was 92.5–94°.

1-Methyl-3-phenyloxindole-3-acetonitrile (IIc).—Similar alkylation of 10.5 g. of 1-methyl-3-phenyloxindole with 3.9 ml. (4.6 g.) of chloroacetonitrile, using a solution of 1.2 g. of sodium in 100 ml. of methanol, gave 10.0 g. (81%) of crystals, m.p. 130–132°. A sample recrystallized from methanol had m.p. 133.5–135°; λ_{max}^{Nujol} 4.40, 5.86, and 6.21 μ; and λ_{max}^{EtOH} 256 mμ (ϵ 7450) with inflections at 268 and 287 mμ (ϵ 5310 and 1560, respectively).

Anal. Calcd. for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.38; N, 10.68. Found: C, 77.67; H, 5.11; N, 10.67.

Methyl 1-Benzyl-3-phenyloxindole-3-acetate (IVa).—Alkylation of 5.4 g. of 1-benzyl-3-phenyloxindole with 6 g. of ethyl bromoacetate in a solution of 0.5 g. of sodium in 150 ml. of methanol gave, after 3.5 hr. of reflux, evaporation, and treatment of the cooled residue with water, a viscous oil which was extracted with ether. After the ether solution had been washed with water, dried over magnesium sulfate, and evaporated to smaller volume, it deposited, in three crops, a total of 5.7 g.

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(22) E. C. Horning, V. L. Stromberg, and H. A. Lloyd, *J. Am. Chem. Soc.*, **74**, 5153 (1952).

(23) W. Herz and G. Caple, *J. Org. Chem.*, **29**, 1691 (1964). Before the appearance of this article we investigated several other uses of this keto acid and its esters and of similar 4-(carboethoxymethyl)-4-phenyl-1-tetralone, syntheses for which are included in the Experimental part.

(24) Calibrated melting points were obtained using a stirred, Thomas–Hoover-type oil bath. Infrared spectra were recorded using Perkin-Elmer double-beam apparatus, and ultraviolet spectra were measured with Beckman recording spectrophotometer.

(25) G. Palazzo and V. Rosnati, *Gazz. chim. ital.*, **82**, 584 (1952); *Chem. Abstr.*, **47**, 12347 (1953); M. E. Speeter, U. S. Patent 2,759,935 (1956); *Chem. Abstr.*, **51**, 2050 (1957); J. F. Bunnett, T. Kato, R. R. Flynn, and J. A. Skorcz, *J. Org. Chem.*, **28**, 1 (1963).

(85%) of crystals: m.p. 105–107°, raised by recrystallization from ether to 107–108°; $\lambda_{\max}^{\text{Nujol}}$ 5.75, 5.83, and 6.18 μ; $\lambda_{\max}^{\text{EtOH}}$ 256 mμ (ϵ 7370) with inflections at 266 and 280 mμ (ϵ 5740 and 1850, respectively).

Anal. Calcd. for $C_{24}H_{21}NO_3$: C, 77.60; H, 5.70; N, 3.77. Found: C, 77.33; H, 5.65; N, 3.91.

Attempts to hydrogenolyze the N-benzyl group in this compound, by 10-hr. shaking of 10.3 g. of the ester with 5 g. of 20% palladium on charcoal in 250 ml. of acetic acid at 80–90° under 50 p.s.i. of hydrogen pressure, resulted in very slow absorption; the product, after evaporation of the filtered solution, was not crystalline. Hydrolysis of this material with hydrochloric–acetic acids (5-hr. reflux) gave a crude mixture and, through fractionation with sodium bicarbonate solution and crystallization from ether–ethyl acetate, a product, colorless crystals, m.p. 223.5–225°, whose analysis indicated that the benzyl group was intact and that one of the benzene rings had been reduced.

Anal. Calcd. for $C_{23}H_{25}NO_3$: C, 76.00; H, 6.93; N, 3.85. Found: C, 76.05; H, 6.97; N, 3.95.

The spectra further showed that the reduced aryl ring was probably the benzo group of the oxindole nucleus: $\lambda_{\max}^{\text{Nujol}}$ 5.75, 6.16 μ, and intact monosubstituted phenyl at 701 cm.$^{-1}$; $\lambda_{\max}^{\text{EtOH}}$ 252, 257, and 264 mμ (ϵ 200, 250, and 180, respectively).

Methyl 1-Methyl-3-benzyloxindole-3-acetate (VIa).—A solution of 1.9 g. (0.0825 g.-atom) of sodium in 150 ml. of methanol was treated first with 16 g. (0.0675 mole) of 1-methyl-3-benzyloxindole,[15] which led to formation of a greenish yellow color, and then with 14 g. (0.084 mole) of ethyl bromoacetate. After the initial, mildly exothermic reaction was complete, the solution was refluxed 3 hr. The work-up was the same as in the preceding experiment, giving slowly crystallizing yellow oil, and eventually, through ether trituration, 9.9 g. (48%) of colorless crystals. Recrystallization from ether gave pure material: m.p. 92–93°; $\lambda_{\max}^{\text{Nujol}}$ 5.75, 5.85, and 6.19 μ; $\lambda_{\max}^{\text{EtOH}}$ 254 mμ (ϵ 7970) with inflections at 262 and 284 mμ (ϵ 6690 and 1590, respectively).

Anal. Calcd. for $C_{19}H_{19}NO_3$: C, 73.76; H, 6.19; N, 4.53. Found: C, 73.65; H, 6.34; N, 4.58.

By alkylation of the appropriate, respective 1,3-disubstituted oxindoles[15] with ethyl bromoacetate or chloroacetonitrile in the presence of sodium methoxide, according to the foregoing procedures, there were also prepared the following compounds.

1-Methyl-3-benzyloxindole-3-acetonitrile (VII) was recrystallized from ether: m.p. 119–120°; $\lambda_{\max}^{\text{Nujol}}$ 4.42, 5.83, and 6.19 μ; $\lambda_{\max}^{\text{EtOH}}$ 255 mμ (ϵ 6910) with inflections at 266 and 286 mμ (ϵ 4960 and 1170, respectively).

Anal. Calcd. for $C_{18}H_{16}N_2O$: C, 78.23; H, 5.84; N, 10.14. Found: C, 78.39; H, 5.88; N, 10.11.

Methyl 1-methyl-3-(*p*-chlorophenyl)oxindole-3-acetate (IVb) was obtained as colorless crystals after recrystallization from methanol: m.p. 118–119°; $\lambda_{\max}^{\text{Nujol}}$ 5.75, 5.85, and 6.20 μ; $\lambda_{\max}^{\text{EtOH}}$ 257 mμ (ϵ 7710) with inflections at 230 and 285 mμ (ϵ 14,300 and 1760, respectively). The sample was either slightly solvated or consisted partly of the corresponding ethyl ester.

Anal. Calcd. for $C_{18}H_{16}ClNO_3$: C, 65.56; H, 4.89; N, 4.25. Calcd. for $C_{19}H_{18}ClNO_3$: C, 66.37; H, 5.28; N, 4.07. Found: C, 66.49, 66.62; H, 4.86, 4.87; N, 4.26.

Methyl 1-methyl-3-(*p*-chlorobenzyl)oxindole-3-acetate (VIb) also appeared to be solvated, and/or to some extent mixed with corresponding ethyl ester: colorless crystals from ether; m.p. 115–118°; $\lambda_{\max}^{\text{Nujol}}$ 5.74, 5.85, and 6.18 μ; $\lambda_{\max}^{\text{EtOH}}$ 255 mμ (ϵ 8510) with inflection at 283 mμ (ϵ 1750).

Anal. Calcd. for $C_{20}H_{20}ClNO_3$: C, 67.12; H, 5.63; N, 3.91. Found: C, 67.43; H, 5.56; N, 4.02.

1-Methyl-3-phenyloxindole-3-acetaldehyde. A. Crude. 1-Methyl-3-phenyl-3-(*β*,*β*-diethoxyethyl)oxindole (IId) was prepared by alkylation of 9.6 g. of 1-methyl-3-phenyloxindole with 10 g. of bromoacetal in the presence of 2.1 g. of sodamide in 300 ml. of toluene. The reaction was stirred and refluxed 5 hr.; the greater part of the reaction appeared to be complete after *ca.* 2 hr. After treatment of the cooled, light brown suspension with water, addition of ether, and separation, the organic solution was washed with three portions of water, dried over magnesium sulfate, filtered, and evaporated. The residual yellow oil crystallized partly. With the aid of a small amount of ether, the crystals of by-product, **1-methyl-3-phenyldioxindole**, were removed; this material (*ca.* 1 g. or less), after recrystallization from ether, had m.p. 142–143° (lit.[26] m.p. 139°); $\lambda_{\max}^{\text{Nujol}}$ 2.98, 5.85, and 6.18 μ; $\lambda_{\max}^{\text{EtOH}}$ 258 mμ (ϵ 6250); and was identical (melting point, mixture melting point, and spectra) with an authentic sample prepared by reaction of N-methylisatin with an equivalent amount of phenyllithium.[27]

Anal. Found: C, 75.37; H, 5.47; N, 5.94.

The oil (*ca.* 9 g.) remaining after removal of this by-product and evaporation of the solvent, did not crystallize, but was shown by hydrolysis to consist mainly of the expected acetal.

When alkylation of 5.0 g. of 1-methyl-3-phenyloxindole with 6 ml. of bromoacetal was carried out using a solution of 0.7 g. of sodium in 150 ml. of methanol, refluxing 3.5 hr., there was isolated 2.8 g. of 1-methyl-3-phenyldioxindole, and the yield of crude acetal was quite low.

B. Hydrolysis.—Crude acetal from A (9 g.) was dissolved in 150 ml. of methanol, 40 ml. of concentrated hydrochloric acid, and 60 ml. of water, and the solution was allowed to stand at room temperature overnight. After decanting away from a small amount of gum, the solution was diluted with 2000 ml. of water, and the yellow oil separating was extracted with ether. The ether solution was washed with two portions each of dilute sodium hydroxide solution and water, was dried over magnesium sulfate, and was evaporated. The crude aldehyde, obtained in nearly quantitative yield, did not crystallize, nor did its corresponding oxime prepared by usual method, and therefore was characterized as the **2,4-dinitrophenylhydrazone**, separating nearly quantitatively as yellow crystals. Recrystallization from ethanol–ethyl acetate gave a pure sample: m.p. 221–223°; $\lambda_{\max}^{\text{Nujol}}$ 3.02, 5.83, and 6.18–6.27 μ.

Anal. Calcd. for $C_{23}H_{19}N_5O_5$: C, 62.02; H, 4.30; N, 15.72. Found: C, 62.04; H, 4.29; N, 15.65.

1-Methyl-3-(2,3-dibromopropyl)-3-phenyloxindole.—Exothermic reaction occurred when 6 ml. (8.4 g., 0.0695 mole) of allyl bromide was added to a solution of 1.4 g. (0.061 g.-atom) of sodium and 11.1 g. (0.05 mole) of 1-methyl-3-phenyloxindole in 150 ml. of methanol. The solution was refluxed 3.3 hr. and reduced to a small volume *in vacuo*, and the cooled residue was treated with water; the aqueous solution was then neutral. The resulting oil was extracted with ether; the ether solution was washed with several portions of water, dried over magnesium sulfate, and evaporated. The crude 3-allyl compound (IIa) did not crystallize, and so was characterized by bromination as follows. A solution of 9.5 g. of the oil in *ca.* 50 ml. of benzene was treated, while cooling to moderate the exothermic effect, with a similar solution of 7 g. of bromine, which was consumed very rapidly; a small amount of hydrogen bromide was evolved, and a heavy oil deposited. The solution, after addition of ether, was washed with sodium bicarbonate solution and water, dried over magnesium sulfate, and evaporated. The crude oil crystallized in the presence of ether; the crystals (5.2 g.), after ether trituration, had m.p. 105–109°. Further recrystallization (ether) raised the melting point to 112.5–114.5°, $\lambda_{\max}^{\text{Nujol}}$ 5.83 and 6.17 μ, $\lambda_{\max}^{\text{EtOH}}$ 258 mμ (ϵ 7740) and inflection at 289 mμ (ϵ 1510). The analysis, together with the observed formation of some hydrogen bromide during bromination, indicated that this product may have been contaminated with a certain amount of 5-bromo compound.

Anal. Calcd. for $C_{18}H_{17}Br_2NO$: C, 51.09; H, 4.05; N, 3.31; Br, 37.8. Found: C, 50.4; H, 3.81; N, 3.15; Br, 39.5.

Hydrolysis of Oxindole-3-acetic Esters and Oxindole-3-acetonitriles to Oxindole-3-acetic Acids.—Two procedures were used in the preparation of **1-methyl-3-phenyloxindole-3-acetic acid** (VIII).

A. Acid hydrolysis of 20 g. of methyl 1-methyl-3-phenyloxindole-3-acetate, with 300 ml. of glacial acetic acid and 500 ml. of concentrated hydrochloric acid, was effected by 5-hr. reflux, after which the solution was poured into 3 l. of ice and water and the product was allowed to crystallize. The crude colorless acid was collected, washed with two portions of water, and dried; the yield of material, m.p. 174–176°, was 15.9 g. (34%). Recrystallization from ethyl acetate gave a pure sample: m.p. 176–178°; $\lambda_{\max}^{\text{Nujol}}$ bonded OH and 5.80, 5.91, and 6.19 μ; $\lambda_{\max}^{\text{CHCl}_3}$ 5.84 and 6.19 μ, with a shoulder 5.70 μ; $\lambda_{\max}^{\text{EtOH}}$ 256 mμ (ϵ 7930) with inflection at 284 mμ (ϵ 1860).

Anal. Calcd. for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.63; H, 5.39; N, 5.05, 4.86.

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[26] See F. K. Beilstein, "Handbuch der organischen Chemie," Vol. 21, I, 1935, p. 464.

[27] See J. M. Bruce, *J. Chem. Soc.*, 2366 (1959). Also formed in our reaction and separated from the dioxindole by fractional crystallization (ether) was 1-methyl-3,3-diphenyloxindole, m.p. 177–178°; *cf.* F. J. Myers and H. G. Lindwall, *J. Am. Chem. Soc.*, **60**, 2153 (1938).

B. Alkaline hydrolysis of the methyl ester with a 12% solution of sodium hydroxide in aqueous methanol (2.5:1) by refluxing 5 hr., or with 30% aqueous potassium hydroxide solution (refluxed 4 hr.) gave, after acidification in each case, the same acid as obtained in A, m.p. 176–178°, mixture melting point undepressed, spectra identical with that of acid from A.

C. Hydrolysis of 1-methyl-3-phenyloxindole-3-acetonitrile with hydrochloric and acetic acids, as described under A, also gave the same acid, m.p. 176–178°, identical with that obtained from A and B.

A sample of the acid (2 g.) was re-esterified by refluxing 4 hr. with 250 ml. of saturated, methanolic hydrogen chloride. After removing the excess reagent *in vacuo* and treating the cooled residue with water, the product was extracted with ether; the ether solution was washed with dilute sodium hydroxide solution and with water and was dried over magnesium sulfate. Evaporation of most of the ether gave colorless crystals, m.p. 95–96°, mixture melting point with the polymorphic original **methyl 1-methyl-3-phenyloxindole-3-acetate (IIb)** undepressed, infrared spectra identical.

The corresponding **anhydride (IX)** of 1-methyl-3-phenyloxindole-3-acetic acid was prepared by refluxing a solution of 2 g. of the acid in 70 ml. of acetic anhydride for 3.5 hr. Evaporation of the excess reagent, trituration, and recrystallization of the residue with ethyl acetate gave colorless crystals: m.p. 170–172° after drying *in vacuo* at 80°; $\lambda_{\max}^{\text{Nujol}}$ 5.62, 5.81–5.84, and 6.18 μ; $\lambda_{\max}^{\text{EtOH}}$ 256 mμ and an inflection at 289 mμ.

Anal. Calcd. for $C_{34}H_{28}N_2O_5$: C, 74.98; H, 5.18; N, 5.14. Found: C, 75.02; H, 5.20; N, 5.20.

Corresponding **amides** were prepared by reaction of the corresponding acid chloride with amines. For example, after a solution of 2.2 g. of 1-methyl-3-phenyloxindole-3-acetic acid in 100 ml. of thionyl chloride and 3 drops of pyridine had been refluxed 1 hr., the excess reagent was distilled *in vacuo;* the crude acid chloride, an orange oil, was dissolved in benzene, the benzene was distilled *in vacuo,* and the residue, again in benzene, was combined with a benzene solution of the appropriate amine in excess. Upon completion of the reaction and 1-hr. standing, the products were isolated by usual procedures and purified by recrystallization from ether.

N-Methyl-1-methyl-3-phenyloxindole-3-acetamide (Xa) was obtained as colorless crystals: m.p. 136.5–138°; $\lambda_{\max}^{\text{Nujol}}$ 3.01, 5.83, and 6.09–6.18 μ; $\lambda_{\max}^{\text{EtOH}}$ 256 mμ (ε 8080) with inflections at 262 and 283 mμ (ε 7290 and 1950, respectively).

Anal. Calcd. for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.36; H, 6.04; N, 9.37.

N,N-Dimethyl-1-methyl-3-phenyloxindole-3-acetamide (Xb) was obtained as colorless crystals: m.p. 140–141.5°; $\lambda_{\max}^{\text{Nujol}}$ 5.84, 6.10, and 6.20 μ; $\lambda_{\max}^{\text{EtOH}}$ 257 mμ (ε 7940) with inflections at 265 and 281 mμ (ε 6640 and 2170, respectively).

Anal. Calcd. for $C_{19}H_{20}N_2O_2$: C, 74.00; H, 6.54; N, 9.09. Found: C, 74.25; H, 6.70; N, 9.28.

Through the same acidic hydrolysis procedure (A), from corresponding esters and nitriles, there were obtained XIa and XIIa.

1-Benzyl-3-phenyloxindole-3-acetic acid (XIa), colorless crystals from ether, had m.p. 176–178°; $\lambda_{\max}^{\text{Nujol}}$ bonded OH and 5.75, 5.88, and 6.20 μ; and $\lambda_{\max}^{\text{EtOH}}$ 256 mμ (ε 7600) with inflection at 283 mμ (ε 1720).

Anal. Calcd. for $C_{23}H_{19}NO_3$: C, 77.29; H, 5.36; N, 3.92. Found: C, 77.34; H, 5.54; N, 3.88.

1-Methyl-3-benzyloxindole-3-acetic acid (XIIa) from hydrolysis of nitrile VII, colorless crystals (from ether), had m.p. 149–150.5°; $\lambda_{\max}^{\text{Nujol}}$ bonded OH and 5.77, 5.94–6.01, and 6.20 μ; $\lambda_{\max}^{\text{CHCl}_3}$ intense and broad peak at 5.85 with moderate shoulders at 5.73 and 6.04 mμ; and $\lambda_{\max}^{\text{EtOH}}$ 255 mμ (ε 8030) with inflections at 265 and 285 mμ (ε 6360 and 1760, respectively).

Anal. Calcd. for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.02; H, 5.86; N, 4.80, 4.73.

From hydrolysis of 6.5 g. of ester VIa, XIIa was also obtained as colorless crystals (5.7 g.): m.p. and m.m.p. 149–151° with preceding sample; $\lambda_{\max}^{\text{Nujol}}$ 5.71–5.74, 5.95–6.02, and 6.20 μ; $\lambda_{\max}^{\text{CHCl}_3;\ \text{EtOH}}$ the same as with the first sample.

Anal. Found: C, 73.22; H, 5.86; N, 4.73.

Solid-state (Nujol) infrared spectra of this acid showed rather remarkable variations in exact positions and relative strengths of carbonyl peaks, depending only upon the technique, concentration, etc., used in preparing mulls, these apparently being due to minor differences in degree of molecular association. It was, however, possible to obtain virtually identical curves with samples from different sources if the materials were prepared and measured in simultaneous, fairly reproducible fashion.

Esterification of the acid with methanolic hydrogen chloride, as with acid VIII, gave again ester VIa, undepressed mixture melting point and identical infrared spectra.

1-Methyl-3-(*p*-chlorophenyl)oxindole-3-acetic acid (XIb) was recrystallized from ethyl acetate after trituration with ether: m.p. 207–209°; $\lambda_{\max}^{\text{Nujol}}$ bonded OH, 5.80–5.87 (broad, unresolved), and 6.19 μ; $\lambda_{\max}^{\text{EtOH}}$ 256 mμ (ε 7870) with inflections at 230 and 280 mμ (ε 14,350 and 2250, respectively).

Anal. Calcd. for $C_{17}H_{14}ClNO_3$: C, 64.66; H, 4.47; N, 4.44. Found: C, 64.80; H, 4.48; N, 4.52.

1-Methyl-3-(*p*-chlorobenzyl)oxindole-3-acetic acid (XIIb), after reprecipitation from sodium bicarbonate solution, gave colorless crystals from ether: m.p. 181–182.5°; $\lambda_{\max}^{\text{Nujol}}$ bonded OH and strong peaks 5.72, 5.94–5.99, and 6.18 μ; $\lambda_{\max}^{\text{EtOH}}$ 255 mμ (ε 8050) with inflections at 221, 263, and 282 mμ (ε 17,020, 4920, and 1740, respectively).

Anal. Calcd. for $C_{18}H_{16}ClNO_3$: C, 65.55; H, 4.89; N, 4.25. Found: C, 66.11; H, 4.89; N, 4.08.

Infrared spectra of this acid in solid state tended to show the same peculiarities as were observed with those of 1-methyl-3-benzyloxindole-3-acetic acid. The spectrum in chloroform, like that of the 3-benzyl acid, had an intense, rather broad band at 5.75–5.84 μ, as well as a less intense peak at 6.19 μ.

1-Methyl-3-(2-pyridylmethyl)oxindole-3-acetic Acid (XIIe). A. Alkylation of 10.4 g. of 1-methyl-3-(2-pyridylmethyl)oxindole[15] was carried out by adding it to a solution of 1.2 g. of sodium in 200 ml. of methanol, after which 3 ml. of chloroacetonitrile was added and the solution was refluxed 3 hr. After evaporation of most of the methanol, treatment of the suspension with water, extraction of the crude product with ether, and subsequent threefold washing of the ether solution with water, drying over magnesium sulfate, and evaporation of the ether, there was obtained 8 g. of orange, oily nitrile (VIIb) which could not be induced to crystallize.

B. Hydrolysis.—The crude nitrile was dissolved in 50 ml. of concentrated hydrochloric acid, and the solution was refluxed 4 hr. After dilution with 900 ml. of water, the orange solution was neutralized with sodium bicarbonate. The cream-colored solid, deposited after the suspension had been kept at 0°, was collected and discarded. Evaporation of the clarified, aqueous solution then gave a mixture of sodium chloride and crude organic material, which was leached with 1 l. of boiling ethyl acetate. The ethyl acetate solution was dried (magnesium sulfate) and evaporated to smaller volume, and the crystals which deposited were collected, yield 1.6 g. (12%) of yellowish crystals, m.p. 210–223° dec. Recrystallization from methanol afforded a pure sample: colorless needles; m.p. 232.5–235° dec.; $\lambda_{\max}^{\text{Nujol}}$ broad zwitterionic bands and 5.78–5.86 (doublet, unresolved), 6.17, and 6.22 μ; $\lambda_{\max}^{\text{EtOH}}$ 255 mμ (ε 10,810) with inflections at 262 and 282 mμ (ε 10,220 and 1840, respectively).

Anal. Calcd. for $C_{17}H_{16}N_2O_3$: C, 68.90; H, 5.44; N, 9.45. Found: C, 68.89; H, 5.45; N, 9.22.

1-Methyl-3-benzyl-5,6-dimethoxyoxindole-3-acetic Acid (XIIc). A. Alkylation of 1-methyl-3-benzyl-5,6-dimethoxyoxindole[15] with ethyl bromoacetate was carried out by adding to a solution of 2.0 g. of potassium in *t*-butyl alcohol, first 5.0 g. of the oxindole and then 15 g. of the bromo ester and, after the initial exothermic reaction was finished, refluxing 3.5 hr. Distillation of solvent *in vacuo*, addition of water to the cooled residue, extraction of the oil with ether, and evaporation of the water-washed, dried, and filtered ether solution gave crude red oil (VIc) which did not crystallize.

B. Hydrolysis of 2.8 g. of crude product from A by refluxing 3 hr. with 150 ml. of 15% potassium hydroxide solution and sufficient ethanol to dissolve the material initially at boiling temperature, followed by acidification of the cooled, clarified solution, gave brownish yellow oil which did not crystallize at first after having been extracted with ether. The crude acid was reprecipitated from an ether-washed sodium hydroxide solution and again extracted with ether, and the ether solution was washed with water, dried over magnesium sulfate, and allowed to evaporate slowly. The least soluble, viscous gum which deposited crystallized after decantation of the supernatant ether solution and addition of a small amount of ethyl acetate. Trituration with and recrystallization from this solvent gave *ca.* 0.3 g. of colorless crystals: m.p. 166–168°, 168–170°; $\lambda_{\max}^{\text{Nujol}}$ 5.77, 5.97–6.03, and 6.17; $\lambda_{\max}^{\text{MeOH}}$ 209 and 275 mμ (ε 32,720 and 5980, respectively) with inflection at 297 mμ (ε 5170).

Anal. Calcd. for $C_{20}H_{21}NO_5$: C, 67.59; H, 5.96; N, 3.94. Found: C, 67.27; H, 6.02; N, 3.95.

1-Methyl-3-(3,4-dimethoxybenzyl)oxindole-3-acetic Acid (XIId). A. Alkylation of 6.0 g. of 1-methyl-3-(3,4-dimethoxybenzyl)oxindole[15] with 6 ml. of ethyl bromoacetate was carried out using a solution of 1.3 g. of sodium in methanol, as described under methyl 1-methyl-3-benzyloxindole-3-acetate; the crude product, 6.6 g. of yellow oil (VId) could not be induced to crystallize.

B. Hydrolysis of 5.6 g. of crude oil from A by refluxing 3 hr. with 100 ml. of 10% sodium hydroxide solution and *ca.* 30 ml. of ethanol to aid dissolution, and subsequent acidification of the chilled, clarified solution, gave several crops, totaling 4.1 g., of yellowish crystals, m.p. *ca* 190–200°, after collection, washing with water, and air drying. Recrystallization from ethyl acetate gave colorless crystals: m.p. 215–218°; $\lambda_{\max}^{\text{Nujol}}$ 5.75, 5.98–6.01, and 6.21 μ; $\lambda_{\max}^{\text{MeOH}}$ 232 and 256 mμ (ε 10,600 and 7620, respectively) with inflections at 276 and 285 mμ (ε 4600 and 3710, respectively).

Anal. Calcd. for $C_{20}H_{21}NO_5$: C, 67.59; H, 5.96; N, 3.94. Found: C, 67.41; H, 6.03; N, 3.92.

The same acid was obtained in lower yield by hydrochloric–acetic acid hydrolysis of the crude ester, followed by extraction of an ether solution of crude product with dilute sodium hydroxide and reacidification of the alkaline solution.

1-Phenyl-3-methyloxindole-3-acetic Acid (XVIII). A. Alkylation of 4.0 g. of 1-phenyl-3-methyloxindole[15] with 6 g. of ethyl bromoacetate was carried out by adding first the oxindole and then the bromo ester to a solution of 0.5 g. of sodium in 100 ml. of methanol, and refluxing 3 hr. After evaporation of methanol and treatment of the residue with water, the product was extracted with ether. The ether solution was washed with several portions of water, dried over magnesium sulfate, and evaporated. The crude ester XVII, after stripping of ethyl bromoacetate *in vacuo,* weighed 6.9 g.: yellow oil which could not be induced to crystallize; $\lambda_{\max}^{\text{CHCl}_3}$ 5.78–5.82 and 6.19 μ; $\lambda_{\max}^{\text{EtOH}}$ 246 mμ (ε 6950).

B. Hydrolysis of the crude ester oxindole from A with hydrochloric–acetic acids gave a low yield of the corresponding acid, and was better carried out using 100 ml. of a 5% solution of sodium hydroxide in 1:1 aqueous methanol for 3.2 g. of the ester and refluxing 5 hr. Acidification of the cooled, diluted solution with hydrochloric acid gave rather readily crystallizing, crude, yellow acid, which was collected, washed with water, and air dried, 2.4 g. yield. Recrystallization from ethyl acetate (Norit) gave pure material: colorless crystals; m.p. 200–203° dec.; $\lambda_{\max}^{\text{Nujol}}$ 5.81 (shoulder 5.77), 5.96, and 6.18 μ; $\lambda_{\max}^{\text{MeOH}}$ 246 mμ (ε 12,810) with inflection 276 mμ (ε 1620); $\lambda_{\min}$ 225 mμ (ε 5850).

Anal. Calcd. for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.54; H, 5.59; N, 5.23.

Re-esterification of this acid with methanolic hydrogen chloride gave crude, neutral oil having spectra virtually the same as the crude ester prepared in A.

Methyl (1-Phenyloxindole-3)glyoxylate.—To a suspension of dry sodium methoxide (from 0.7 g. of sodium) in 100 ml. of dry ether were added 4.4 g. of N-phenyloxindole and 6 ml. of ethyl oxalate. Mildly exothermic dissolution of the methoxide was followed soon by separation of a bright yellow salt. After standing stoppered at room temperature 3 days, the salt was collected, washed with dry ether, and dissolved in 200 ml. of water. The aqueous solution was acidified with dilute hydrochloric acid. The enol separated initially as orange oil and gradually became crystalline with a small amount of ether present. The crystals were collected, washed with water, air dried, and triturated with a small amount of methanol. The yield of product, m.p. 104–107°, was 2.6 g. (42%). Recrystallization of a sample from methanol gave yellow crystals: m.p. 110.5–112°; $\lambda_{\max}^{\text{Nujol}}$ 5.76, 6.05 (moderate), and 6.18–6.25 μ (doublet); $\lambda_{\max}^{\text{MeOH}}$ 248, 265, and 309 mμ (ε 15,310, 17,160, and 8410, respectively) with inflection at 328 mμ (ε 6970). The compound gave a very deep purple ferric chloride test.

Anal. Calcd. for $C_{17}H_{13}NO_4$: C, 69.14; H, 4.44; N, 4.74. Found: C, 68.92; H, 4.59; N, 4.72.

When the acylation was carried out using sodium methoxide from 4.1 g. of sodium, 34 g. of N-phenyloxindole, and 68 ml. of ethyl oxalate, and allowed to stand only 4 hr. before working up, the accompanying ester exchange was incomplete; there was isolated 16.3 g. (*ca* 33%) of yellow enolic crystals: m.p. 62–65° (recrystallization did not raise the melting point beyond 74°); $\lambda_{\max}^{\text{Nujol}}$ 5.75, 6.02, and 6.16–6.23 μ; ultraviolet spectrum nearly the same as the pure methyl ester. This material, equally suitable for further work, appeared to be a mixture of methyl and ethyl glyoxylates.

Anal. Found: C, 69.11; H, 4.65; N, 4.38.

Methyl 1-Phenyloxindole-3-acetate (XIX).—Following the procedure used in hydrogenolysis of 1-phenyl-3-hydroxymethyleneoxindole,[15] a solution of 5.8 g. of enolic ester from the preceding experiment in 250 ml. of ethyl acetate and 8 ml. of glacial acetic acid was treated with 1.0 g. of 10% palladium on charcoal and shaken under 50 p.s.i. of hydrogen pressure at 60° for 3 hr. Evaporation of the filtered solution gave yellow, viscous oil; even after being washed (as an ether solution) with dilute alkali and water, dried, and stripped of solvent, this material refused to crystallize. A sample, dried *in vacuo,* showed $\lambda_{\max}^{\text{CHCl}_3}$ 5.73–5.82 (unresolved doublet) and 6.18 μ and $\lambda_{\max}^{\text{MeOH}}$ 247 mμ (ε 9900) with inflection at 313 μ (ε 980), showing the presence of oxindole and ester groups.

1-Phenyl-3,4-dihydrocarbostyril-4-carboxylic Acid (XX).—A solution of 2.4 g. of crude ester from the preceding experiment in 50 ml. each of concentrated hydrochloric acid and glacial acetic acid was refluxed 5 hr. When the cooled solution was poured over ice and water, a crystalline solid separated; this material was collected, washed with water, and air dried. After removal of a small amount of yellow impurity by trituration with ether, the crystals (1.8 g.) had m.p. *ca* 220–225° dec. A pure sample was obtained by recrystallization from ethyl acetate: colorless crystals; m.p. 253–254° dec.; $\lambda_{\max}^{\text{Nujol}}$ 5.85, 6.10, and 6.36 μ with a lesser sharp peak 6.28 μ; $\lambda_{\max}^{\text{MeOH}}$ 206, 214, 230, 284, and 340 mμ (ε 34,140, 33,780, 27,930, 5930, and 340, respectively); soluble in sodium bicarbonate solution.

Anal. Calcd. for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 72.20; H, 4.20; N, 5.28.

The corresponding **methyl ester** was prepared by 3.5-hr. reflux of a solution of 1.0 g. of the acid in 150 ml. of saturated absolute methanolic hydrogen chloride. Isolation of the neutral fraction, by the usual procedure, gave an ether solution which upon slow evaporation deposited yellowish crystals, m.p. 165–167.5°. Recrystallization from ether–ethyl acetate gave a pure sample: m.p. 166–168°; $\lambda_{\max}^{\text{Nujol}}$ 5.78 (sharp), 6.00 (intense), and 6.29 μ, with sharp, lesser peaks at 6.20 and 6.25 μ; $\lambda_{\max}^{\text{MeOH}}$ 205, 231, 286, and 344 mμ (ε 44,520, 24,330, 5860, and 5060, respectively) and inflection at 261 mμ (ε 4570).

Anal. Calcd. for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.73; H, 4.97; N, 5.17.

The infrared spectrum of a chloroform solution of the ester also clearly showed the characteristic ester (5.78 μ), six-membered lactam (6.04 μ), and phenyl (6.23–6.28 μ) peaks.

The spectra (Nujol) of both acid and ester showed sharp peaks at 695 and 705 cm.$^{-1}$ (monosubstituted phenyl).

β-(1-Methyl-3-phenyloxindole-3)propionitrile (XXIa).—A solution of 13.7 g. of 1-methyl-3-phenyloxindole and 2 ml. of 40% methanolic benzyltrimethylammonium methoxide in 83 ml. of tetrahydrofuran was treated with 5 ml. of acrylonitrile during a period of a few minutes, while stirring and cooling in ice as necessary to prevent the temperature from rising above 20°, after which the solution was allowed to stand at 20–25° for 1.2 hr. Acidification (18% hydrochloric acid) and dilution with water of the chilled solution afforded crystalline product which was collected, washed with water, and air dried; the yield of slightly discolored product, m.p. 160–164°, was 16.9 g. (quantitative). Recrystallization from methanol raised the melting point to 166–167°: $\lambda_{\max}^{\text{Nujol}}$ 4.44 (weak), 5.88, and 6.21 μ; $\lambda_{\max}^{\text{EtOH}}$ 256 mμ (ε 7590) with inflection at 286 mμ (ε 1590).

Anal. Calcd. for $C_{18}H_{16}N_2O$: C, 78.23; H, 5.84; N, 10.14. Found: C, 78.14; H, 5.65; N, 9.93.

β-(1-Methyl-3-benzyloxindole-3)propionitrile (XXIb).—Cyanoethylation of 10 g. of 1-methyl-3-benzyloxindole was carried out by the procedure described in the preceding experiment. After dilution of the acidified reaction solution, a yellow oil separated and was extracted with ether. The ether solution was washed with several portions of water, dried over magnesium sulfate, and filtered. Slow evaporation of the ether solution provided part of the product in the form of crystals, 4.5 g. of material in several crops, m.p. *ca.* 65–75°. The remainder of the crude material (8.9 g.), a yellow oil after evaporation of the ether, still consisted mainly of product since it provided on methanolysis the corresponding methyl ester. A sample of the crystals, after recrystallization from ether, had m.p. 79–81°; $\lambda_{\max}^{\text{Nujol}}$ 4.44 (weak), 5.83, and 6.18 μ; $\lambda_{\max}^{\text{MeOH}}$ 206 and 257 mμ (ε 30,600 and 7160, respectively) with inflection at 278 mμ (ε 1730).

Anal. Calcd. for $C_{19}H_{18}N_2O$: C, 78.59; H, 6.25; N, 9.65. Found: C, 78.66; H, 6.16; N, 9.41.

β-(1-Methyl-3-phenyloxindole-3)propionic Acid (XXII).—Hydrolysis of 6.4 g. of β-(1-methyl-3-phenyloxindole-3)propionitrile by refluxing for 5 hr. a solution of the nitrile in 60 ml. each of glacial acetic acid and concentrated hydrochloric acid gave, upon subsequent dilution with 1500 ml. of water, a colorless, viscous oil which crystallized on standing. The crystals were collected, washed with water, and air dried; the yield of crude acid, m.p. 159–162°, was 6.3 g. After recrystallization from ethyl acetate there were obtained colorless crystals: m.p. 162–164°, $\lambda_{\max}^{\text{Nujol}}$ 5.81–5.84 (unresolved doublet) and 6.20 μ, $\lambda_{\max}^{\text{EtOH}}$ 255 mμ (ϵ 7630) with inflection at 282 mμ (ϵ 1840). The compound was soluble in sodium bicarbonate solution.

Anal. Calcd. for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.21; H, 5.50; N, 4.73.

Methyl β-(1-Methyl-3-benzyloxindole-3)propionate.—A solution of 3.5 g. of crude, oily β-(1-methyl-3-benzyloxindole-3)propionitrile in 100 ml. of saturated methanolic hydrogen chloride was refluxed 3 hr. After evaporation of excess reagent and treatment of the cooled residue with water, an oil separated and was extracted with ether. The ether solution was washed with water, dried, and evaporated. The residual oil solidified and, on trituration with ether, gave 3.0 g. of crystals: m.p. 105–110°, raised on further recrystallization from ether to 112–115°; $\lambda_{\max}^{\text{Nujol}}$ 5.78, 5.87 (intense doublet), and 6.20 μ; $\lambda_{\max}^{\text{EtOH}}$ as for nitrile, 205 and 256 mμ (ϵ 33,200 and 7620, respectively) and inflection at 284 mμ (ϵ 1530).

Anal. Calcd. for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.41; H, 6.80; N, 4.25.

With ethanolic hydrazine, refluxed for 3 hr., evaporated, and the residue treated with water, the ester formed a gummy **hydrazide**, which crystallized after extraction with ether; trituration with ether and recrystallization from ethyl acetate gave colorless crystals: m.p. 157–159.5°; $\lambda_{\max}^{\text{Nujol}}$ 3.01 (strong), broad, shouldered peak 5.92–6.00, and 6.20 μ; $\lambda_{\max}^{\text{MeOH}}$ 255 mμ (ϵ 7030) with inflection at 284 mμ (ϵ 1430).

Anal. Calcd. for $C_{19}H_{21}N_3O_2$: C, 70.56; H, 6.55; N, 13.00. Found: C, 70.99; H, 6.62; N, 12.79.

3-Carboxy-3-(*o*-N-methylaminophenyl)-1-indanone Lactam (XIII).—A mixture of 4.4 g. of 1-methyl-3-phenyloxindole-3-acetic acid and 73 g. of polyphosphoric acid was stirred and heated on a steam cone 5 hr. The resulting deep wine red solution was cooled and hydrolyzed with ice and water. The solid which formed was collected, washed with water, suspended in dilute sodium hydroxide solution, and again filtered, washed with water, and air-dried. The crude, neutral product (2.4 g.) was recrystallized from ethyl acetate–ether: colorless crystals; m.p. 190–192°; $\lambda_{\max}^{\text{Nujol}}$ unresolved doublet 5.82–5.90 μ, sharp peak at 6.19 μ, and no peak at 697 cm.$^{-1}$; $\lambda_{\max}^{\text{EtOH}}$ 245 and 286 mμ (ϵ 17,450 and 3880, respectively) and shoulder at 293 mμ (ϵ 3670).

Anal. Calcd. for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.39; H, 5.02; N, 5.28.

When the cyclization was carried out by heating the acid (3 g.) and polyphosphoric acid (40 g.) mixture on a hot plate, with stirring, for 0.5 hr., to a maximum temperature of 153° (reached in 20 min. and maintained for a brief period), there was obtained the same product in somewhat better (2.2 g.) yield.

1-Carboxy-1-(*o*-N-methylaminophenyl)indan Lactam (XIV).—A solution of 1.5 g. of crystals from the preceding experiment in 200 ml. of glacial acetic acid was treated with 0.5 g. of 10% palladium on charcoal and shaken under 50 p.s.i. of hydrogen pressure at 80° for 6 hr. Evaporation of the filtered solution gave a yellow oil, crystallizing in the presence of ether and affording discolored crystals (0.7 g.), m.p. *ca.* 111–115°, which, after recrystallization from ether, were colorless and had m.p. 115–117°, $\lambda_{\max}^{\text{Nujol}}$ 5.90 and 6.21 μ, $\lambda_{\max}^{\text{MeOH}}$ 257 mμ (ϵ 7960) with inflections at 266 and 280 mμ (ϵ 6610 and 1880, respectively), both spectra again being characteristic of an N-methyloxindole.

Anal. Calcd. for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62. Found: C, 81.86; H, 6.25; N, 5.53.

3-Carboxy-3-(*o*-N-methylaminophenyl)-1-tetralone Lactam (XVa).—Cyclization of 10.2 g. of 1-methyl-3-benzyloxindole-3-acetic acid with 160 g. of polyphosphoric acid was carried out by heating to *ca.* 110° for 20 min. Hydrolysis of the brown solution was followed by extraction of the crude product with ether–ethyl acetate; the organic solution was washed with successive portions of 5% sodium hydroxide solution and water, dried over magnesium sulfate, and evaporated. Trituration of the pale yellow, crystalline residue with ether gave 8.2 g. (87%) of slightly discolored crystals, m.p. *ca.* 154°. A pure sample, after recrystallization from ether, had m.p. 153.5–155°; $\lambda_{\max}^{\text{Nujol}}$ 5.89 and 5.95 μ (close doublet), 6.18 μ, and no peak at 700 cm.$^{-1}$; $\lambda_{\max}^{\text{EtOH}}$ 251 and 295 mμ (ϵ 18,810 and 2350, respectively) with inflection at *ca.* 300 mμ (ϵ 2110).

Anal. Calcd. for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05. Found: C, 77.66; H, 5.59; N, 4.99.

3-Carboxy-3-(*o*-N-methylaminophenyl)tetralin Lactam (XVIa).—Hydrogenation of 5.0 g. of compound from the preceding experiment in 250 ml. of glacial acetic acid in the presence of 1.0 g. of 10% palladium on charcoal at 80° under 50-lb. hydrogen pressure for 3.5 hr. and evaporation of the filtered solution gave a brown oil, crystallizing upon addition of ether and giving, after trituration with ether, 4.0 g. of nearly colorless crystals: m.p. 116–122° (several recrystallizations from ether raised the melting point to 125–127°), $\lambda_{\max}^{\text{Nujol}}$ 5.82 (intense) and 6.17 μ, $\lambda_{\max}^{\text{MeOH}}$ 253 and 273 mμ (ϵ 8670 and 2730, respectively) with inflection at 284 mμ (ϵ 1470).

Anal. Calcd. for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32. Found: C, 81.50; H, 6.52; N, 5.27.

3-Carboxy-3-(*o*-N-methylaminophenyl)-6,7-dimethoxy-1-tetralone Lactam (XVb).—Polyphosphoric acid (35 g.) cyclization of 2.4 g. of 1-methyl-3-(3,4-dimethoxybenzyl)oxindole-3-acetic acid at 100° for 0.5 hr., hydrolysis of the very deep red solution (ice–water), extraction (ether–ethyl acetate) of the crude product, and isolation of the neutral material as usual by washing with dilute sodium hydroxide solution, drying, and evaporating, gave 1.3 g. of crude crystals, m.p. 219–227°. Recrystallization from ethyl acetate provided a pure sample: faintly yellowish crystals; m.p. 230–232°; $\lambda_{\max}^{\text{Nujol}}$ 5.84, 5.97, and 6.24 μ; $\lambda_{\max}^{\text{MeOH}}$ 238, 279, and 318 mμ (ϵ 25,930, 11,150, and 7250, respectively).

Anal. Calcd. for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68, N, 4.15. Found: C, 71.05; H, 5.65; N, 4.28.

4-Carboxy-4-(*o*-N-methylaminophenyl)-1-tetralone Lactam (XXIII).—Cyclization of 4.0 g. of β-(1-methyl-3-phenyloxindole-3)-propionic acid with 140 g. of polyphosphoric acid was promoted by gradually raising the temperature of the stirred mixture to 145° over a period of about 1 hr.; the resulting dark brown solution was cooled and hydrolyzed, and the ether-extracted product was washed with dilute alkali and water, as usual. The dried (magnesium sulfate) ether solution, upon evaporation, gave crude neutral material, trituration of which with ether provided 2.7 g. of crystals, m.p. 156–163°. Recrystallization from ethanol gave colorless crystals: m.p. 169–171°; $\lambda_{\max}^{\text{Nujol}}$ 5.89–5.95 μ (poorly resolved), with weak shoulders at 5.80 and 5.89 μ, 6.18 μ (sharp, with lesser peak 6.24 μ), and no peak at 700 cm.$^{-1}$; $\lambda_{\max}^{\text{EtOH}}$ 250 and 289 mμ (ϵ 17,600 and 3930, respectively).

Anal. Calcd. for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05. Found: C, 77.89; H, 5.44; N, 5.15.

The hydrogenolysis of this compound is described below in another connection.

4-Carbethoxy-4-phenyl-1-tetralone Oxime (XXV). A.—Esterification of 50 g. of 4-phenyl-1-tetralone-4-carboxylic acid[23,28] with a solution of 140 ml. concentrated sulfuric acid and 10 ml. of 30% oleum in 3000 ml. of sodium-dried ethanol, was carried out by refluxing 3 days. After distillation of most of the excess ethanol *in vacuo* and addition of ice–water to the cooled residue, the crude neutral product was isolated as usual; the yield of ester, m.p. 86–89° after crystallization from ether, was 40.4 g. (73%). After recrystallization from ether a sample had m.p. 89.5–91°, $\lambda_{\max}^{\text{Nujol}}$ 5.78 and 5.92 μ, and $\lambda_{\max}^{\text{EtOH}}$ 248 and 290–294 mμ (ϵ 11,930 and 2040, respectively).

Anal. Calcd. for $C_{19}H_{18}O_3$: C, 77.53; H, 6.16. Found: C, 77.50; H, 6.34.

B.—The oxime was obtained by 10-min. reflux of a solution of 19 g. of the ester from A, 48 g. of hydroxylamine hydrochloride, and 19 g. of sodium hydroxide in 285 ml. of water and 300 ml. of ethanol. The oily product which separated upon dilution with water was extracted with ether. The ether solution was washed with several portions of water, dried over magnesium sulfate, and evaporated. The residue, crystallizing from aqueous ethanol, gave 19.0 g. (95%) of crystals, m.p. *ca.* 130°. A pure sample was obtained by recrystallization from ethanol: colorless crystals; m.p. 136–138°; $\lambda_{\max}^{\text{Nujol}}$ 3.07–3.09 (broad, moderate) and 5.77 μ (intense); $\lambda_{\max}^{\text{EtOH}}$ 256 mμ (ϵ 13,410) with shoulders at 220 and 298 mμ (ϵ 22,470 and 640, respectively).

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[28] This keto acid, m.p. 159–160°, was prepared in 54% yield by cyclization of either 2,2-diphenylglutaric acid or the corresponding anhydride with concentrated sulfuric acid at room temperature (5–12 hr.).

Anal. Calcd. for $C_{19}H_{19}NO_3$: C, 73.76; H, 6.19; N, 4.53. Found: C, 73.73; H, 5.96; N, 4.70.

5-Carbethoxy-5-phenyl-2,3,4,5-tetrahydro-1H-benzo[6,7]azepin-2-one (XXVI).—A mixture of 14 g. of oxime from the preceding experiment and 427 g. of polyphosphoric acid was heated, while stirring, to a maximum temperature of 140° during a period of 1.2 hr.; for most of this time (0.8 hr.) the temperature was kept at *ca.* 110–120°. After ice–water hydrolysis of the cooled, brown solution, the brick red solid was collected, washed with water, dried (10.6 g., crude yield), and recrystallized from ethanol. There were obtained 8.2 g. (57%) of crystals, m.p. 174–177°. Further recrystallization from ethanol gave a pure sample: m.p. 176–178° (sintered at 173°); $\lambda_{\max}^{\text{Nujol}}$ 3.15, 3.27, 5.77, 5.96, and (moderate doublet) 6.21–6.29 μ; $\lambda_{\max}^{\text{EtOH}}$ 230 mμ (ϵ 11,190).

Anal. Calcd. for $C_{19}H_{19}NO_3$: C, 73.76; H, 6.19; N, 4.53. Found: C, 73.98; H, 6.04; N, 4.53.

When the rearrangement was carried out on a larger scale, similarly, heating 43 g. of oxime with 1300 g. of polyphosphoric acid and proceeding as described above, the first two fractions of ethanol-recrystallized material, totaling 25 g. (58%), consisted of the same benzazepinone, m.p. *ca.* 176°. The third crop of crystals obtained from the ethanol filtrates, proved to be a by-product, **4-carboxy-4-(*o*-aminophenyl)-1-tetralone lactam (XXIX)**: 6.7 g. (17%) of slightly pink crystals; m.p. 198–202°, raised by further ethanol recrystallization to 204–206°; mixture melting point with an authentic specimen, obtained as described below, was undepressed; infrared spectra were identical.

β-(3-Phenyloxindole-3)propionic Acid (XXVIII).—A solution of 2 g. of benzazepinone ester, from the preceding experiment, in 40 ml. of concentrated hydrochloric acid and 20 ml. of glacial acetic acid, was refluxed 3 hr. After dilution with ice and water, the oily material was extracted with ether. The ether solution was washed with water and extracted with dilute sodium hydroxide solution. Acidification of the aqueous alkaline solution, and extraction of the resulting oily acid with ether, several-fold washing (water) of the ether solutions, drying over magnesium sulfate, evaporation, and trituration of the residue with ether provided 0.9 g. of crystals: m.p. 135–137°, not raised on further recrystallization from ether; $\lambda_{\max}^{\text{Nujol}}$ broad, bonded OH and NH bands and 5.73, 5.88 (difficultly resolved doublet), and 6.15 μ; $\lambda_{\max}^{\text{EtOH}}$ 223–226 and 277–282 mμ (ϵ 5840 and 1810, respectively) with a shoulder at 265 mμ (ϵ 5120).

Anal. Calcd. for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.73; H, 5.71; N, 4.90.

A sample of the corresponding **ethyl ester** was prepared by 3-hr. reflux of the acid (0.8 g.) with 100 ml. of 10% ethanolic sulfuric acid; the neutral product, isolated as usual and recrystallized from aqueous ethanol, had m.p. 85–86°; $\lambda_{\max}^{\text{Nujol}}$ bonded 3.17-μ NH band, 5.76, 5.84 (doublet), and 6.16 μ; $\lambda_{\max}^{\text{EtOH}}$ 252 mμ (ϵ 7570) with inflections at 264 and 282 mμ (ϵ 5230 and 1620, respectively).

Anal. Calcd. for $C_{19}H_{19}NO_3$: C, 73.76; H, 6.19; N, 4.53. Found: C, 73.71; H, 6.23; N, 4.56.

4-Carboxy-4-(*o*-aminophenyl)-1-tetralone Lactam (XXIX).—Treatment of a small sample (*ca.* 1 g.) of β-(3-phenyloxindole-3)-propionic acid with *ca.* 20–30 parts (by weight) of polyphosphoric acid at 110° for 1 hr., isolation of the neutral product, and recrystallization from ethanol gave colorless crystals: m.p. 204–206°; $\lambda_{\max}^{\text{Nujol}}$ bonded NH and 5.85–5.92 (poorly resolved doublet, with shoulder 5.98 μ) and 6.17–6.23 μ (moderate); $\lambda_{\max}^{\text{EtOH}}$ 248 and 289 mμ (ϵ 17,190 and 3480, respectively); identical with the by-product obtained in the above preparation of benzazepinone ester.

Anal. Calcd. for $C_{17}H_{13}NO_2$: C, 77.55; H, 4.98; N, 5.32. Found: C, 77.94; H, 4.83; N, 5.10.

1-Carboxy-1-(*o*-aminophenyl)tetralin Lactam (XXX).—Hydrogenolysis of 2 g. of keto lactam from the preceding experiment in 250 ml. of glacial acetic acid in the presence of 2 g. of 10% palladium on charcoal for 7 hr. at 50-p.s.i. hydrogen pressure and *ca.* 40°, followed by filtration of the catalyst, evaporation of the solvent, and ether trituration of the residue, afforded 2 g. of crude, grayish discolored crystals, m.p. 220–224°. A methanol-recrystallized sample had m.p. 228–229.5°; $\lambda_{\max}^{\text{Nujol}}$ 5.86 and 6.18 μ, as well as bonded NH bands, and no peak at 700 cm.$^{-1}$; and $\lambda_{\max}^{\text{EtOH}}$ 251 mμ (ϵ 7630) with inflections at 273 and 282 mμ (ϵ 2030 and 1640, respectively).

Anal. Calcd. for $C_{17}H_{15}NO$: C, 81.90; H, 6.06; N, 5.62. Found: C, 81.86; H, 6.10; N, 5.59.

1-Carboxy-1-(*o*-N-methylaminophenyl)tetralin Lactam (XXIV).—Identical specimens of this spirotetralin oxindole were obtained from two sources. (A) Hydrogenolysis of 1.8 g. of 4-carboxy-4-(*o*-N-methylaminophenyl)-1-tetralone lactam in glacial acetic acid in the presence of 1.5 g. of 10% palladium on charcoal for 6.5 hr. and evaporation of the filtered solution, gave crude material, which was dissolved in ether with the aid of a little acetone. The organic solution was washed with successive portions of dilute hydroxide and water, dried over magnesium sulfate, and evaporated. The residue crystallized when dissolved in warm ether, giving 1.0 g. of crystals, m.p. 145–147°. (B) Methylation of 0.75 g. of 1-carboxy-1-(*o*-aminophenyl)tetralin lactam in 200 ml. of toluene with excess (10 ml.) methyl iodide in the presence of 1 g. of sodium hydride, refluxing and stirring for a total of 7 hr., followed by addition of water to the cooled suspension, washing of the ether-diluted organic layer with water, and evaporation of the dried solution, gave 0.6 g. of crystals, m.p. 146–147°.

Recrystallization of each of these samples (ether) gave pure material: m.p. 147–148°; mixture melting point undepressed; infrared spectra (Nujol) identical, with $\lambda_{\max}$ 5.85 and 6.18 μ; $\lambda_{\max}^{\text{EtOH}}$ 255 mμ (ϵ 8040) and inflection at 280 mμ (ϵ 2080).

Anal. Calcd. for $C_{18}H_{17}NO$: C, 82.10; H, 6.51; N, 5.32. Found: C, 82.02; H, 6.63; N, 5.11.

1-Methyl-5-carbethoxy-5-phenyl-2,3,4,5-tetrahydrobenzo[6,7]-azepin-2-one (XXVII).—A suspension of 5 g. of 5-carbethoxy-5-phenyl-2,3,4,5-tetrahydro-1H-benzo[6,7]azepin-2-one and *ca.* 3 g. of sodium hydride in 750 ml. of toluene was stirred and refluxed 1 hr., cooled, treated with 23 ml. of methyl iodide, and again stirred and refluxed 5.5 hr. The cooled, filtered, water-washed, and magnesium sulfate dried solution, upon evaporation to smaller volume afforded (four crops) a total of 4.9 g. (94%) of crystals, melting point varying from 133–135° to 131–133°. A sample, recrystallized from ethanol, had m.p. 135–137°; $\lambda_{\max}^{\text{Nujol}}$ 5.78 and 6.00 μ (intense, sharp) and a moderate, sharp peak at 6.22 μ; the ultraviolet spectrum (EtOH) was a strong absorption curve, showing no true maxima but inflected at *ca.* 233 mμ (10,660).

Anal. Calcd. for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.22; H, 6.55; N, 4.43.

Hydrolysis and rearrangement of 0.6 g. of this lactam ester with 50 ml. of concentrated hydrochloric acid and 35 ml. of glacial acetic acid (refluxed 4 hr.), followed by dilution, extraction of crude product with ether, and evaporation of a dried organic solution obtained by ether extraction of ether-washed, reacidified dilute alkaline solution, afforded crystals of **β-(1-methyl-3-phenyloxindole-3)propionic acid (XXIIa)**: recrystallized from ethyl acetate, m.p. 161–163°; m.m.p. (with sample obtained as described above) 161–164°; infrared spectra (Nujol) of the specimens were identical.

1-Methyl-5-hydroxymethyl-5-phenyl-2,3,4,5-tetrahydrobenz-[6,7]azepine (XXXI).—A solution of 2.2 g. of N-methylbenzazepinone ester from the preceding experiment and 6 g. of lithium aluminum hydride in 400 ml. of tetrahydrofuran was stirred and refluxed 5.5 hr., and left standing at room temperature overnight. Cautious addition of 30 ml. of water to the cooled, stirred suspension and 1-hr. additional stirring gave a white, hydrolyzed suspension, which was filtered. The filtrate was dried over potassium carbonate and evaporated. The crude, oily base was dissolved in ether and extracted with cold, dilute hydrochloric acid. The acid solution was made basic with dilute potassium hydroxide; the regenerated base was extracted with ether; the ether solution was washed with water, dried over potassium carbonate, and evaporated. Since the base could not be obtained in acceptable crystalline form, it was identified by preparation of a sample of the **picrate**, yellow crystals from ethanol, m.p. 152–154°.

Anal. Calcd. for $C_{24}H_{24}N_4O_8$: C, 58.06; H, 4.87; N, 11.29. Found: C, 58.09; H, 5.09, N, 11.26.

There was no absorption in the carbonyl region in the infrared spectra of crude base or picrate.

Half-Ester of β,β-Diphenyladipic Acid. A. 1-Phenyl-1-(carbethoxymethyl)butyrolactone[23,29] was prepared by Reformatsky reaction of 279 g. (1.35 mole) of ethyl β-benzoylpropionate with 260 g. (1.56 moles) of ethyl bromoacetate and 120 g. of hydro-

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[29] *Cf.* T. Kubota and T. Matsura, *J. Inst. Polytech., Osaka City Univ.*, **C4**, 112 (1953). Because of a tendency for violent, exothermic reaction after an initial induction period of 0.5–1.0 hr., it is inadvisable to use ether as solvent, or to add all the material at once, in this and similar condensations.

chloric acid activated, washed, and dried zinc in 300 ml. of dry benzene. The reaction was initiated by adding *ca.* 10% of the reagents and a trace of iodine to the vigorously stirred, heated zinc–benzene suspension and, after the exothermic complex formation had begun, the remaining reagents were added (simultaneously) at such a rate, with continued stirring, as to maintain a controllable rate of reflux. Following the period of spontaneous reaction, the mixture was refluxed and stirred 1.5 hr. The cooled organic layer, decanted from remaining zinc with the aid of ether and methanol, was treated first with cold water, then washed with successive portions of 20% acetic acid, 3% sodium hydroxide solution, and water, and was dried over magnesium sulfate. The solvents were evaporated, and the crude, oily lactone ester (yield 251 g., 75%), showing strong infrared spectral peaks 5.62 and 5.79 μ, and 696 cm.$^{-1}$, was used without further purification.

B. **Ethyl β,β-Diphenyl-δ-carboxyvalerate.**—A solution of 224 g. (0.90 mole) of 1-phenyl-1-(carbethoxymethyl)butyrolactone from A in 600 ml. of dry benzene was added, over a period of 0.9 hr., to a stirred, ice-chilled suspension of 266 g. (2.0 moles) of anhydrous aluminum chloride in 2000 ml. of benzene. The mixture was stirred at ice temperature 3 hr. longer, then stirred while allowing the temperature to rise slowly to room temperature for 1–1.5 hr.; if there was an appreciable quantity of unconsumed aluminum chloride present, the solution was decanted away from it before being left to stand at room temperature overnight. The solution was poured over ice and excess hydrochloric acid. After shaking and separating the layers, the aqueous solution was extracted with several portions of ether. The combined organic solutions were washed with successive portions of dilute hydrochloric acid and water, and then extracted with 5% potassium hydroxide solution. Acidification of the aqueous, alkaline solution gave crude product as an oil. This material was extracted with ether; the ether solution was washed with water, dried over magnesium sulfate, and evaporated to smaller volume, whereupon crystallization occurred. Collected in three crops and recrystallized from ether, the acid ester totaled 142 g. (48%), m.p. 101–104°. Further recrystallization from ether gave pure material, m.p. 106.5–108.5°, λ_{max}^{Nujol} 5.74 and 5.83 μ, together with bonded OH and intense 703- and 916-cm.$^{-1}$ peaks.

Anal. Calcd. for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79. Found: C, 73.61; H, 6.73.

No other crystalline products were isolated from the crude residue of the acid fraction; from the original organic layer there was obtained 53 g. of neutral oil which did not crystallize.

C.—A different form of **acid ester** was obtained when 54 g. (0.218 mole) of the ester lactone from A was condensed with benzene in the presence of 120 g. (0.90 mole) of aluminum chloride, following the same procedure as in B but then allowing the mixture to stand 3 days. The acidic fraction of the product, after reprecipitation from dilute potassium hydroxide solution, was found to be a mixture. Trituration with ether gave the least soluble component, which proved to be a by-product, evidently **3-phenyl-Δ^2-hexene-1,6-dioic acid**: 9.2 g.; m.p. 152–153° after ether recrystallization; λ_{max}^{Nujol} 5.85 and 5.90 μ in addition to bonded OH, ionic bands, and shoulders in the 6.10-μ region).

Anal. Found: C, 65.42; H, 6.30.

The filtrate remaining after removal of this material was evaporated. The residual, impure, greenish brown oil was leached with *ca.* 500 ml. of boiling cyclohexane; the resulting solution, after decanting away from the residual brown gum, upon gradual evaporation deposited, first more brown oil, and then several crops of discolored crystals, totaling 31 g. (43%), m.p. *ca.* 78–83°. Purified by repeated recrystallization from ether–cyclohexane, this acid ester consisted of colorless crystals: m.p. 93–95°; λ_{max}^{Nujol} 3.07 (moderate–intense), 5.76, and 5.84 μ; solid-state spectrum was quite different from that of acid ester obtained in B, showing a weaker 700-cm.$^{-1}$ peak and no peak at or near 916 cm.$^{-1}$. Like the product from B, this compound was soluble in sodium bicarbonate solution. The mixture melting point was indecisive, but the infrared spectra of the two forms of acid ester in chloroform solution were identical, and a strong 5.86-μ shouldered peak, indicating that the two forms are polymorphic.

Anal. Calcd. for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79. Found: C, 73.46; H, 6.84.

Hydrolysis of samples of acid ester from these reactions, with 10% sodium hydroxide solution (3-hr. reflux) in each case after acidification gave **β,β-diphenyladipic acid**: m.p. 188.5–191° after ethyl acetate recrystallization (lit.[23] m.p. 187–189°); λ_{max}^{Nujol} 5.80 and 5.86 μ, together with bonded OH band and a moderate, broad peak at 870 cm.$^{-1}$.

4-Phenyl-4-(carbethoxymethyl)-1-tetralone and Oxime XXXII. A. **Cyclization** of 107.5 g. of acid ester (B) from the preceding experiment with 2000 ml. of concentrated sulfuric acid at room temperature gave a dark-colored solution after stirring 0.5 hr. The sulfuric acid solution was allowed to stand 4 hr. longer, then poured with stirring over ice. The resulting oil was extracted with ether. The ether solution was washed with successive portions of water, dilute potassium hydroxide solution, and water, dried over magnesium sulfate, and evaporated. The neutral material solidified in the presence of ether, giving, after collection with the aid of this solvent, 70.5 g. (69%) of crystals, m.p. 55–60°. A sample after further recrystallization from ether had m.p. 60–62°; λ_{max}^{Nujol} 5.78, 5.94, and 6.23 μ; and λ_{max}^{EtOH} 249 and 292 mμ (ϵ 11,740 and 1990, respectively).

Anal. Calcd. for $C_{20}H_{20}O_3$: C, 77.90; H, 6.54. Found: C, 78.11; H, 6.54.

The **2,4-dinitrophenylhydrazone** was recrystallized from ethanol–ethyl acetate: red-orange crystals; m.p. 159–161°; λ_{max}^{Nujol} 5.75 and 6.18–6.25 μ.

Anal. Calcd. for $C_{26}H_{24}N_4O_6$: C, 63.92; H, 4.95; N, 11.47. Found: C, 64.07; H, 5.00; N, 11.38.

The same keto ester (1.2 g.) as a crude oil, identified by preparation of an identical 2,4-dinitrophenylhydrazone, was obtained by cyclization of 3.3 g. of isomeric acid ester (C) from the preceding experiment with 30 ml. of concentrated sulfuric acid.

Hydrolysis of 2 g. of the tetralone ester with 100 ml. of 5% potassium hydroxide solution (refluxed 3 hr.) and acidification, gave **4-phenyl-4-(carboxymethyl)-1-tetralone** (1.9 g.): m.p. 181–182° after ether recrystallization (lit.[23] m.p. 175–177°); λ_{max}^{Nujol} 5.84 and 5.92 μ as well as a bonded OH band (lit.[23] λ_{max} 5.85 and 5.92 μ); λ_{max}^{EtOH} 250 and 294 mμ (ϵ 11,500 and 2220, respectively). This acid (10 g.) was also obtained by acidification of the aqueous potassium hydroxide wash from cyclization of 108 g. of acid ester (B) as described above.

In another run, cyclization of 90 g. of acid ester was carried out using 1500 ml. of concentrated sulfuric acid as before, and after work-up, the ether solution of crude, neutral product was let evaporate gradually. In this case, there first crystallized a by-product, 6 g. (8%) of **spiro[3-indanone-1,1′(4′)-tetralone]** (XXXVII): m.p. 156–158° (lit.[23] m.p. 152–154°) after recrystallization from ether; λ_{max}^{Nujol} 5.87 and 5.95 μ (lit.[23] 5.85 and 5.92 μ).

Anal. Found: C, 81.74; H, 5.39.

After removal of this by-product, evaporation of the ether solution of the remaining neutral material gave 25 g. of tetralone ester, m.p. *ca.* 60°, as before.

B. **Oxime XXXII.**—A solution of 5 g. of tetralone ester from A in 80 ml. of ethanol, after being combined with a cold solution of 12.5 g. of hydroxylamine hydrochloride and 5 g. of sodium hydroxide in 75 ml. of water, was refluxed 10 min. The chilled solution deposited crystals, which were collected, washed with water, and dried; the crude oxime (5.5 g.) was recrystallized from ethanol, giving 5.1 g. of colorless crystals, m.p. 124–127°, suitable for further work. Further recrystallization from ethanol raised the melting point to 128–130°: λ_{max}^{Nujol} broad OH band, 5.73 (intense), and 6.22 μ; λ_{max}^{EtOH} 256 mμ (ϵ 12,600) with inflections at 218 and 278 mμ (ϵ 24,890 and 850, respectively).

Anal. Calcd. for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.53; H, 6.50; N, 4.34.

On storage at room temperature for 6–8 months, this oxime gradually decomposed with formation of an orange, viscous oil.

Beckmann rearrangement of 4 g. of oxime from the preceding experiment with 121 g. of polyphosphoric acid was carried out by heating, while stirring, over a period of 1 hr., to a maximum temperature of 130°. Upon hydrolysis of the chilled, brown solution with ice and water, a semisolid was formed which was extracted with ether. The ether solution was washed to neutrality with portions of dilute alkali and water, as usual, dried over magnesium sulfate, and evaporated. The resulting viscous, greenish glass, dissolved in *ca.* 100 ml. of ether and allowed to stand, deposited about 0.5 g. of crystals of by-product, spiro compound **XXXVI**, which were collected and washed with ether; the colorless crystals (m.p. 201–203°) were purified by further recrystallization from ether: m.p. 204–205°; λ_{max}^{Nujol} bonded NH bands at 3.14–3.26 and intense, wide doublet at 5.78 and 5.98 μ, no 700 cm.$^{-1}$ peak; λ_{max}^{EtOH} 242 and 281 mμ (ϵ 21,450 and 2380, respectively) with inflection at 291 mμ (ϵ 2120).

Anal. Calcd. for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.45; N, 5.05. Found: C, 77.61; H, 5.61; N, 5.25.

The remaining crude neutral product (XXXIII) could not be induced to crystallize.

4-Phenyl-4-(β-carboxyethyl)-3,4-dihydro-2-quinolone (XXXIV).—The crude, neutral product remaining from the preceding experiment was dissolved in 25 ml. of glacial acetic acid and 50 ml. of concentrated hydrochloric acid. The solution was refluxed 5 hr. After dilution of the cooled solution, the crude material was taken into ether solution; the ether solution was washed with several portions of water and extracted with 5% sodium hydroxide solution. The alkaline solution was acidified with hydrochloric acid, and the crude acid was again extracted with ether. After the ether solution had been washed with water, dried over magnesium sulfate, and evaporated, the acid crystallized. There was obtained, after ether trituration, *ca.* 0.4 g. of crystals: m.p. 259–260°, raised to 262–263° by recrystallization from methanol; $\lambda_{\max}^{\text{Nujol}}$ broad, bonded NH bands at 3.12–3.27 μ, intense doublet at 5.86 and 6.05 μ, and sharp, moderate peak 6.25 μ; $\lambda_{\max}^{\text{EtOH}}$ 251 mμ (ϵ 11,090) with inflections at 263 and 280 mμ (ϵ 7800 and 2320, respectively).

Anal. Calcd. for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 73.50; H, 5.86; N, 4.79.

Repetition of the steps, beginning with Beckmann rearrangement, leading to this compound did not significantly improve the yield. Attempted spirocyclization of this dihydroquinolone acid (0.4 g.), with polyphosphoric acid at 115–125° as usual, afforded less than 0.1 g. of neutral product consisting, after recrystallization from ether (Norit), of colorless crystals, m.p. 195–200° (softening 154°), evidently a mixture, $\lambda_{\max}^{\text{Nujol}}$ 5.92–5.97 μ (unresolved doubled) and no peak *ca.* 700 cm.$^{-1}$, indicating that the material may have been an impure sample of spirotetralone.

1-Methyl-4-phenyl-4-(β-carbethoxyethyl)-3,4-dihydro-2-quinolone (XXXV). A.—Esterification of 0.25 g. of dihydroquinolone acid from the preceding experiment with a solution of 10 ml. of concentrated sulfuric acid in 200 ml. of ethanol gave, after usual isolation, 0.25 g. of neutral oil which did not crystallize.

B.—N-Methylation of 0.25 g. of ester from A, by refluxing and stirring with 1 g. of sodium hydride and 10 ml. of methyl iodide in 150 ml. of toluene for 7 hr., gave, after treatment with water and isolation of neutral product, 0.2 g. of noncrystalline material.

C.—Hydrolysis of crude product from B, by refluxing 3 hr. with 50 ml. each of glacial acetic and concentrated hydrochloric acids, and isolation of acid by extraction of an ether solution of crude material with dilute base and reacidification, gave crude acid which crystallized and, after filtration with the aid of ether, afforded 0.16 g. of material, m.p. 195–196°. Recrystallization from ether gave a pure sample: m.p. 198.5–199.5°; $\lambda_{\max}^{\text{Nujol}}$ 5.77 and 6.13 μ (intense), as well as a bonded OH, a sharp peak at 6.27 μ and a sharp 701-cm.$^{-1}$ peak; $\lambda_{\max}^{\text{EtOH}}$ 254 mμ (ϵ 10,460) with inflection at 262 mμ (ϵ 8820).

Anal. Calcd. for $C_{19}H_{19}NO_3$: C, 73.76; H, 6.19; N, 4.53. Found: C, 73.99; H, 6.19; N, 4.51.

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Prototropic Rearrangement of a 1,4-Enyne. Products and Mechanism

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The alkaline rearrangement of methyl crepenynate (methyl *cis*-9-octadecen-12-ynoate) proceeds through a *cis*-enallenic intermediate to *trans,cis,trans*- and *trans,cis,cis*-8,10,12-octadecatrienoic acids in 70% yield. The formation of the isolable enallene is base catalyzed, but the second step, resulting in conjugated trienes, is thermal. These conjugated trienoic acids have been cyclized thermally to a disubstituted cyclohexadiene in good yield. The mechanism by which the Δ^{10} double bond of the conjugated triene becomes exclusively *cis* is probably an intramolecular 1,5-proton transfer *via* a cyclic transition state.

In a recent publication from this laboratory,[3] we reported isolation of a new polyunsaturated fatty acid, crepenynic acid, from the seed oil of *Crepis foetida* (family *Compositae*). This new acid was shown to have the structure of *cis*-9-octadecen-12-ynoic acid. In a subsequent publication,[4] we reported that methyl crepenynate (**1**) is readily isomerized by potassium hydroxide in ethylene glycol to an 8,10,12-octadecatrienoic acid (**2a**) in 70% yield. The nonconjugated enyne system was apparently converted completely to conjugated triene systems (**2a**–**3**) when heated with 10% base for 1 hr. at 120°.[4] The conjugated trienes had an infrared spectrum, characterized by maxima at 10.1 and 10.4 μ, different from any of the known geometric isomers of this system. Gas–liquid chromatography (g.l.c.) of the isomerization products showed, in addition to conjugated triene, an unknown peak which had retention characteristics[5] different from those of **2a** and **1**.

It became of interest to explore the mechanism by which this preponderance of one positional isomer is formed, to determine the geometric configuration of the conjugated trienoic acids formed, and to determine the structure of the unknown component which appeared on the gas chromatogram of the isomerization products. Results of such studies provide the basis of the work reported here.

Rearrangement of various types of acetylenic compounds under the influence of alkali has been observed by several groups of workers.[6–10] Allenes and isomeric acetylenes typically have been found as products. The alkali-catalyzed rearrangement of 1,4-enynes has been

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