[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, UNIVERSITY OF MINNESOTA]

A Novel Rearrangement Involving Indole Dimers[1]

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The maleyl and fumaryl derivatives of indole:2-methylindole dimer (Ib) and the maleyl derivatives of skatole:2-methylindole dimer (*cis*-Id) and of indole:2-phenylindole dimer (*cis*-Ic) rearrange under alkaline hydrolysis conditions to the corresponding (2-methyl-3-indole)succinic acid (IIb) in the first three cases, or (2-phenyl-3-indole)succinic acid (IIc) in the latter case. The 2-substituent labels the indole nucleus to which migration of the maleyl or fumaryl group has occurred. Besides by means of the rearrangement, (2-phenyl-3-indole)succinic acid (IIc) has been prepared from the reaction of 2-phenylindole with maleic acid. The corresponding anhydride, (2-phenyl-3-indole)succinic anhydride, has been prepared from the diacid by anhydride exchange with acetic anhydride. For rearrangement to occur, the necessity of a hydrogen on nitrogen of the indole nucleus has been demonstrated. This is shown by the fact that the maleyl and fumaryl derivatives of indole:1,2-dimethylindole dimer (Ie) undergo simple alkaline hydrolysis, without rearrangement, to the dimer and fumaric acid. A mechanism for the rearrangement is proposed in which the maleyl or fumaryl group is transferred intramolecularly through a six-membered spiro ring intermediate from the 1-position of the indoline nucleus to the 3-position of the indole nucleus in the dimer with subsequent depolymerization. The isolation of an isomer of maleyl skatole:2-methylindole dimer, for which the spiro ring structure of the intermediate has been proposed, lends further support to the proposed intermediate in the mechanism. This isomer rearranges under alkaline hydrolysis conditions to the same product (IIb) as maleyl skatole:2-methylindole dimer. Some of the limits of the rearrangement are delineated by the facts that, like maleyl and fumaryldiskatole (VII), maleyl indole:2,5-dimethylpyrrole dimer (VIII) and itaconyldiindole undergo simple amide hydrolysis without rearrangement. Some of the value of the rearrangement, besides in the synthesis of (3-indole)succinic acid (IIa),[4] is illustrated by the fact that both the itaconyl (IX) and citraconyl (*cis*-X) derivatives of indole:2-methylindole dimer rearrange to the same new diacid, for which the 2-methyl-2-(2-methyl-3-indole)succinic acid structure (XI) is proposed. This diacid is different from another new diacid (XII) derived from hydrolysis of the anhydride adduct of 2-methylindole and itaconic anhydride. Likewise, the anhydrides of the two diacids are different.

We have previously shown that rearrangement of maleyldiindole (*cis*-Ia) under alkaline hydrolysis conditions yields (3-indole)succinic acid (IIa).[4] It was established that (3-indole)succinic acid does not form by addition of indole to maleate or fumarate anions, which might have resulted from prior alkaline hydrolysis of maleyldiindole. It follows then that during the rearrangement the 3-position of either the indoline or the indole nucleus of diindole must add to the α,β-unsaturation of the maleyl group.

Two possible reaction mechanisms, both involving six-membered ring intermediates, were considered as most plausible. One mechanism would require that a benzyl hydrogen at the 3-position of the indoline portion of maleyldiindole (*cis*-Ia) be sufficiently acidic so that a benzyl anion is formed, which could undergo intramolecular Michael addition to the maleyl or fumaryl group, forming the bicyclic six-membered ring intermediate (or transition state) III. Cleavage of the acyl-nitrogen bond in III could be concerted with the formation of III (resulting in a transient ketene intermediate) or cleavage could be the result of subsequent amide hydrolysis. In either case, the anion on nitrogen would have to depolymerize by eliminating an indole molecule, thus forming the indolenine IV, which would rapidly tautomerize to (3-indole)succinate IIa anion.

If maleyldiindole rearranges according to this mechanism, then 1-maleylindoline and 1-maleyl-2-methylindoline might undergo a similar cyclization step, perhaps more easily because of the absence of a large hindering substituent at the 2-position. In these cases, however, the (3-indoline)succinic acids should represent stable end products, since the hydrogen or methyl substituents in the 2-position should eliminate less readily as anions than indole. 1-Maleylindoline and 1-maleyl-2-methylindoline were prepared and subjected to the alkaline hydrolysis conditions of the rearrangement. They did not rearrange, but underwent simple amide hydrolysis instead. Indoline and 2-methylindoline were recovered as the picrates in 87 and 89% yields, respectively, along with 74 and 79% yields of fumaric acid, the alkaline isomerization product of maleic acid. Consequently, the validity of the mechanism proposed for the rearrangement of maleyldiindole, in which the maleyl group is transferred intramolecularly from the 1- to the 3- position of the indoline nucleus through intermediates like III, has not been demonstrated in these cases.

1-Maleylindoline crystallized from benzene as a yellow solvent complex containing one molecule

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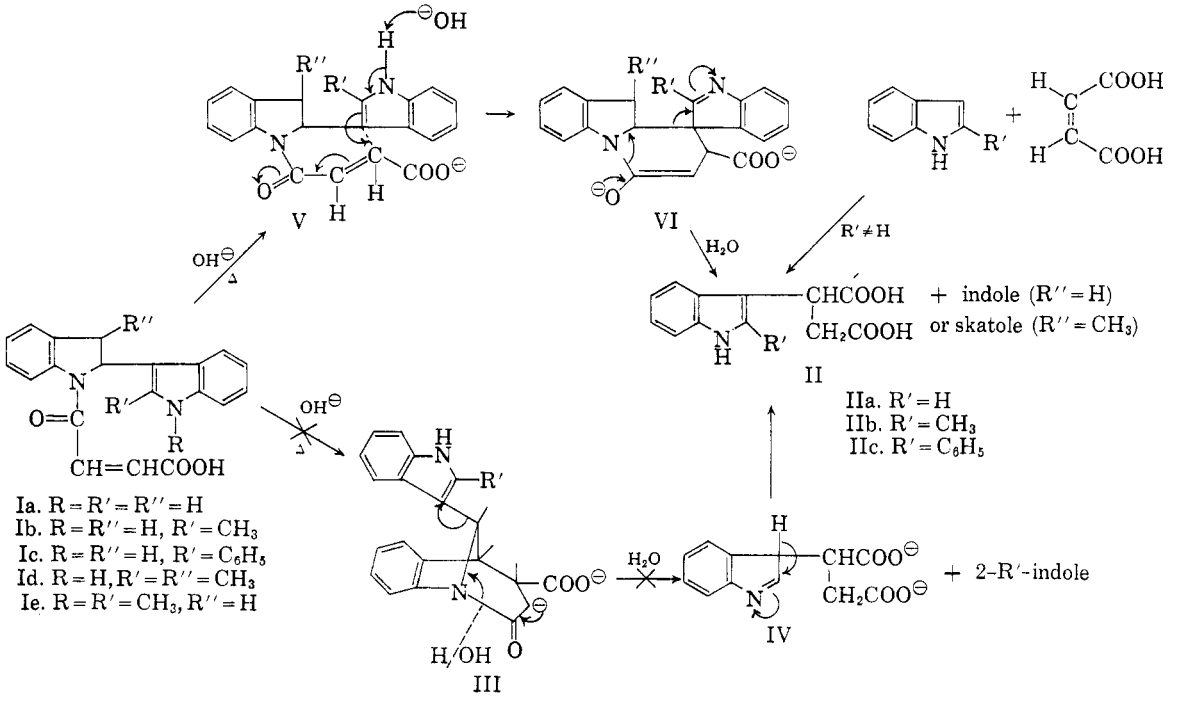
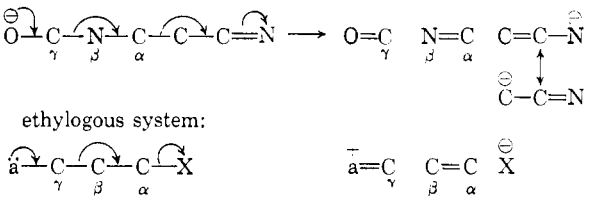
(4) W. E. Noland and C. F. Hammer, *J. Org. Chem.*, **23**, 320 (1958).



of benzene for each two molecules of 1-maleylindoline. When dropped on a hot block, the yellow crystals melt at 128–130°, with the evolution of benzene, and then solidify to the white, benzene-free compound, m.p. 155–156.5° dec. When heated slowly, the yellow crystals turn white and evolve their benzene quantitatively within ten minutes at 100°. The white compound is reconverted to the yellow benzene complex upon recrystallization from benzene. 1-Succinylindoline was also prepared for the purpose of comparison of its physical properties.

The other most plausible mechanism for the rearrangement of maleyldiindole (*cis*-Ia) involves initiation (V) by removal of the acidic proton from nitrogen of the indole nucleus, giving a resonance-stabilized anion, quite probable under the alkaline conditions employed. Although neutral 3-alkylindoles normally undergo electrophilic substitution at the 2- position,[5] and indole anions add preferentially at the 1-position in *inter*molecular Michael additions,[6] steric factors in this *intra*molecular case would favor Michael addition (V) of the indole anion at its 3- position, yielding the six-membered spiro ring intermediate (or transition state) VI. Rapid alkaline hydrolysis of this intermediate (or of the ketene derivable from it by a concerted elimination) and elimination of an indole molecule would then yield (3-indole)succinate(IIa) anion. This elimination reaction is seen to be an example of Grob's "Principle of Ethylogy,"[7] in which a nitrogen atom has replaced a β-carbon atom of the usual ethylogous system.



To test the validity of this mechanism for the rearrangement, it is necessary to label one indole nucleus so that it can be distinguished from the other in the dimer. Conceivably this objective can be accomplished by labeling one of the indole nuclei with isotopic carbon or nitrogen. The presently available method of synthesis of diindole, by acid-catalyzed dimerization of indole, offers no hope, however, of specificity in this regard. Consequently, we turned to the synthesis of mixed indole dimers, which would contain the desired distinguishing label in the form of a substituent on one of the indole nuclei, the location of which must be established unambiguously. This is the subject of our preceding paper.[8]

Both the maleyl and fumaryl derivatives of indole:2-methylindole dimer (Ib) rearranged under alkaline hydrolysis conditions to (2-methyl-3-indole)succinic acid (IIb) in yields of 96% and 87%, respectively. No (3-indole)succinic acid (IIa) was formed, but indole was obtained in yields of 87% and 72%. The fact that both the maleyl and fumaryl derivatives rearrange shows that the steric requirements of the reaction at the double bond are

(5) W. E. Noland and D. N. Robinson, *Tetrahedron*, **3**, 68 (1958).
(6) J. Szmuszkovicz, *J. Am. Chem. Soc.*, **79**, 2819 (1957).
(7) C. A. Grob, *Experientia*, **13**, 126 (1957).
(8) W. E. Noland and C. F. Hammer, *J. Org. Chem.*, **25**, 1525 (1960).

not a dominant factor. Likewise, a 3-methyl substituent on the indoline nucleus does not inhibit the reaction; the maleyl derivative of skatole:2-methylindole dimer (Id) rearranged to (2-methyl-3-indole)succinic acid (IIb, 100%) and skatole (95%). Similarly, the maleyl derivative of indole:-2-phenylindole dimer (Ic) rearranged to (2 phenyl-3-indole)succinic acid (IIc, 86%) and indole (79%). Since (2-phenyl-3-indole)succinic acid was previously unknown, it was prepared independently in 70% yield by warming 2-phenylindole with maleic acid according to a modification of the method of Noland and Lange[9] for (2-methyl-3-indole)succinic acid. (2-Phenyl-3-indole)succinic acid (IIc), which appeared to be unstable and did not crystallize well from other solvents, was best isolated from acetonitrile as a stable, crystalline solvent complex containing one molecule of acetonitrile for each two molecules of the acid. The acid was converted to the corresponding anhydride by anhydride exchange with acetic anhydride.

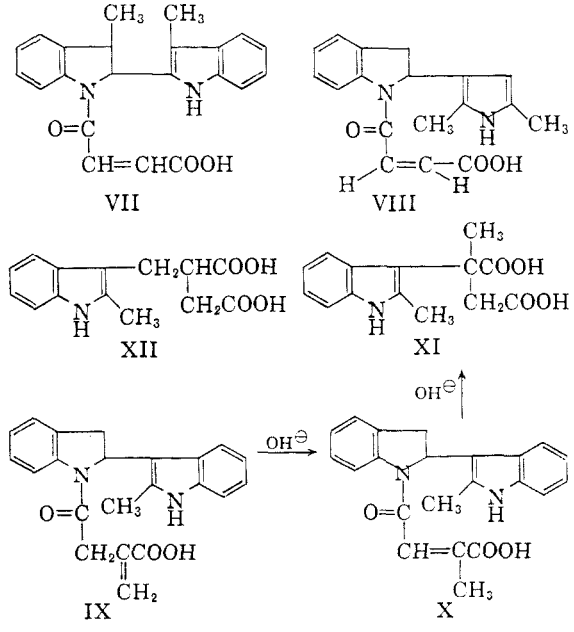
The results of the hydrolysis experiments involving derivatives of mixed indole dimers support the mechanism proposed for the rearrangement in which a maleyl (or fumaryl) group is transferred through intermediates like V and VI from the indoline to the indole nucleus of the dimer. The necessity in the rearrangement for an initiating step in which a proton is removed from nitrogen of the indole nucleus is suggested by experiments in which the N—H group of the indole nucleus is replaced by an N—CH_3 group. Alkaline hydrolysis of both the maleyl and fumaryl derivatives of indole:1,2-dimethylindole dimer (Ie) gave only the regenerated dimer in yields of 98% and 39%, respectively, along with fumaric acid, but no (1,2-dimethyl-3-indole)succinic acid.[8] These results indicate that the rearrangement does not proceed with maleyl and fumaryl derivatives of mixed indole dimers containing substituents other than hydrogen on nitrogen of the indole nucleus.

Of great interest in connection with proposal of VI as an intermediate in the rearrangement is the isolation from acylation of skatole:2-methylindole dimer with maleic anhydride in more polar solvents of a product for which a structure analogous to the keto form of VI has been proposed.[8] This rearrangement product (XXI in the preceding paper[8]) further rearranged under alkaline hydrolysis conditions in the same manner as its isomer, the maleyl derivative of skatole:2-methylindole dimer (Id), to give (2-methyl-3-indole)succinic acid (IIb) in 94% yield, and skatole in 94% yield.

Maleyldiskatole and fumaryldiskatole are reported to undergo alkaline hydrolysis without rearrangement, yielding diskatole and fumaric acid.[10] Since the structure of diskatole has been proved by degradation,[11] its maleyl and fumaryl derivatives will have the corresponding structures (VII). In these cases failure to rearrange is not due to lack of an N—H group on the indole nucleus.

If rearrangement were to occur at the 2- position, a common site for electrophilic substitution in skatole,[5] then structures VII would lead to a six-membered ring intermediate which would possess a driving force for elimination of a skatole molecule. That such rearrangement does not occur may be attributed to the lower nucleophilicity in indoles of a 2- position relative to a correspondingly substituted 3- position. For these diskatole derivatives to cyclize at the 3- position to intermediates analogous to VI would require the sterically less probable formation of a seven-membered ring. Even if such cyclization were to occur, however, a driving force for the elimination phase of the rearrangement would be lacking. Consequently, it is logical that the rearrangement does not occur with diskatole derivatives.

The maleyl derivative of indole:2,5-dimethylpyrrole dimer (VIII) also underwent alkaline hydrolysis without rearrangement, giving the dimer in 85% yield, along with a quantitative yield of fumaric acid.[8] The failure of this derivative to rearrange must be attributed to low nucleophilicity of the 3- position of the 2,5-dimethylpyrrole nucleus, which permits the rate of simple amide hydrolysis to exceed substantially the rate of rearrangement. Perhaps low acidity of the pyrrole N—H, which, unlike the indoles, lacks an *N*-phenyl



(9) (a) W. E. Noland, R. F. Lange, F. B. Stocker, and G. L. Sauer, Paper 10 presented before the Organic Division at the 132nd National Meeting of the American Chemical Society, Sept. 9, 1957, Abstracts, p. 6P; (b) Ronald F. Lange, Ph.D. Thesis, University of Minnesota, June 1958.

(10) O. Diels, K. Alder, and W. Lübbert, *Ann.*, **490**, 277 (1931).

(11) G. F. Smith and A. E. Walters, unpublished work, University of Manchester, England (private communication, Oct. 16, 1958).

substituent, makes anion formation relatively difficult.

The rearrangement described in this paper may have little practical value for the synthesis of (2-substituted-3-indole)succinic acids since they are conveniently prepared directly by addition of 2-substituted indoles to maleic acid.[9] The rearrangement does have value, however, in the synthesis of (3-indole)succinic itself,[4] and may have value in the preparation of (3-indole)propionic acids and their derivatives substituted in any position but the 1- position of the indole nucleus, starting from the appropriate acrylic derivatives of indole dimers. This phase of our research is currently under investigation.

In hope of using the rearrangement to synthesize (3-indole)succinic acids containing additional substituents in the succinic acid sidechain, we have prepared the itaconyl (IX) and citraconyl (*cis*-X) derivatives of indole:2-methylindole dimer and shown that they are different compounds.[8] Both derivatives rearranged under alkaline hydrolysis conditions to the same new diacid, m.p. 223–224.5° dec., in yields of 72% and 37%, along with indole in yields of 53 and 81%, respectively. This diacid is assigned the structure 2-methyl-2-(2-methyl-3-indole)succinic acid (XI), although the alternative structure, 2-methyl-3-(2-methyl-3-indole)succinic acid, has not been rigorously excluded. Assignment of structure XI to the diacid is based on the following plausible assumptions with respect to the structure of its acylated dimer precursors: (1) that, with itaconic anhydride, acylation has occurred at the less sterically hindered and less resonance stabilized, saturated carbonyl group; and (2) that, with citraconic anhydride, acylation has occurred at the less sterically hindered carbonyl group, the one β- to the methyl group.

It is evident that, under the alkaline conditions employed, the double bond of either the itaconyl or the citraconyl derivative has rearranged to the alternative position. That it is the double bond of the itaconyl derivative which has rearranged (into conjugation with both carbonyl groups) is established by the fact that the diacid product, m.p. 223–224.5° dec., is different from another new diacid, m.p. 149–151° dec., obtained by hydrolysis of the anhydride adduct of 2-methylindole and itaconic anhydride. Since the latter was formed under mild, nonalkaline conditions, the double bond of itaconic anhydride is assumed not to have rearranged prior to addition of 2-methylindole; consequently, structure XII appears to be established for the diacid, m.p. 149–151° dec., derived from this anhydride adduct. The anhydride, m.p. 144°, prepared from XI by anhydride exchange with acetic anhydride, like the parent diacids, was different from the anhydride adduct, m.p. 134–135°, from 2-methylindole and itaconic anhydride. The reactions of 2-methylindole with citraconic acid or citraconic anhydride failed to give either the diacids XI or XII or the corresponding anhydrides. Consequently, the rearrangement has synthetic value for the preparation of the diacid XI.

In contrast to the itaconyl derivative of indole:2-methylindole dimer (IX), which underwent double bond isomerization and then rearrangement, itaconyldiindole underwent alkaline hydrolysis without rearrangement, giving diindole in 67% yield, along with mesaconic acid, an isomerization product of itaconic acid, in 81% yield. The failure of itaconyldiindole to rearrange must be attributed to the lower nucleophilicity of the indole nucleus (relative to that of 2-methylindole), combined with a possibly greater rate of hydrolysis of the less hindered amide linkage, a rate which must substantially exceed the combined rates of double bond isomerization and subsequent rearrangement involving nucleophilic attack at a relatively hindered tertiary carbon atom.

Our work on the rearrangement has so far been carried out with hydrolysis under heterogeneous conditions, by refluxing with aqueous 30% hydroxide solution, and the yields have been good. It may be more convenient and desirable from a synthetic standpoint, however, to carry out the rearrangement under homogeneous conditions, in alcoholic alkali. Our experience indicates that (3-indole)succinic acid can be prepared in this way (see Experimental) in as good yield, and in a purer initial state, than by the method previously described.[4] A new and convenient synthesis of (3-indole)succinic acid has recently been reported.[12]

EXPERIMENTAL

Melting points were determined on a calibrated Fisher-Johns hot stage. In this paper, with reference to the melting points of carboxylic acids, "dec." indicates that melting occurred with gas evolution, in the form of steam or carbon dioxide.

Indoline. The procedure of King, Barltrop, and Walley[13] was used. Indole (100.0 g., 0.854 mole) in absolute ethanol (750 cc.) solution was hydrogenated at 100 atm. over Raney nickel at 95–101° for 4 hr. After filtration of the catalyst and removal of the solvent, vacuum distillation yielded a colorless oil (93.6 g., 0.785 mole, 92%), b.p. 65–67° (0.5–1.5 mm.). Fractional vacuum distillation yielded the ultraviolet sample, $n_D^{24.3}$ 1.5866, reported:[14] n_D^{20} 1.5923. $\lambda_{max}^{95\%\ C_2H_5OH}$: 240 m$\mu$ (log ϵ 3.83), 292 (3.35). ν_{NH} 3400 cm.$^{-1}$ on the liquid.

The picrate, after recrystallization from benzene, melted at 174–176° dec., reported:[13,15] 174°.

2-Methylindoline. The procedure of King, Barltrop, and Walley[13] for indoline was used. 2-Methylindole (25.0 g., 0.0190 mole) in absolute ethanol (150 cc.) solution was hydrogenated at 100 atm. over Raney nickel at a maximum temperature of 118° for 4 hr. After filtration of the catalyst and

(12) Y. G. Perron and W. F. Minor, *J. Org. Chem.*, **24**, 1165 (1959).

(13) F. E. King, J. H. Barltrop, and R. J. Walley, *J. Chem. Soc.*, 277 (1945).

(14) J. v. Braun, *Ber.*, **45**, 1285 (1912).

(15) G. Plancher and C. Ravenna, *Atti reale accad. Lincei*, [5]14, I, 632 (1905) [*Chem. Zentr.*, II, 335 (1905)].

removal of the solvent, fractional distillation yielded two principal fractions: (1) 2-methyloctahydroindole (10.03 g., 0.0721 mole, 38%), b.p. 79–84° (19 mm.), $n_D^{28.8}$ 1.4786, reported for *cis*-2-methyloctahydroindole:[16] n_D^{25} 1.4743, and (2) 2-methylindoline (8.51 g., 0.0639 mole, 34%), b.p. 112–114° (19 mm.), $n_D^{28.7}$ 1.5652, reported[17,18]: n_D^{15} 1.5719, $n_D^{23.4}$ 1.5687.

To obtain the ultraviolet sample, the picrate (described in the following section) was made alkaline with 20% sodium hydroxide solution, extracted with ether, and the ether solution washed with 20% sodium hydroxide. Evaporation of the ether and fractional distillation gave the ultraviolet sample, b.p. 108° (17 mm.), n_D^{24} 1.5653. $\lambda_{max}^{95\%\ C_2H_5OH}$: 241 mμ (log ε 3.84), 293 (3.34). ν_{NH} 3390 cm.$^{-1}$ on the liquid.

2-Methylindoline picrate. 2-Methylindoline was added to a solution of picric acid in ether. The crystalline precipitate was recrystallized from benzene, yielding yellow needles, m.p. 159–160°. Our melting point is higher than that reported,[19,20] 150–151°, 151°.

Anal. Calcd. for $C_{15}H_{14}N_4O_7$ (362.29): C, 49.73; H, 3.90; N, 15.47. Found: C, 50.03; H, 3.82; N, 15.31.

1-Maleylindoline. Indoline (10.0 g., 0.0839 mole) was added dropwise to a cold solution of maleic anhydride (8.30 g., 0.0847 mole) in benzene (65 cc.), causing immediate separation of bright yellow crystals (7.75 g., containing 0.0302 mole of 1-maleylindoline, 36%). When dropped on a hot block, the yellow crystals melt at 128–130°, with the evolution of benzene, and then solidify to a white compound, m.p. 155–156.5° dec. The white compound is conveniently obtained from the yellow crystals by heating below the melting point, at 100–110°, to drive off the benzene. Recrystallization from acetonitrile gives white crystals, m.p. 158–159° dec. Recrystallization of the white compound from benzene regenerates the yellow crystals.

(a) 1-Maleylindoline benzene complex, yellow crystals from benzene, m.p. 128–130°. $\lambda_{max}^{95\%\ C_2H_5OH}$: 253 mμ (log ε/2 4.06), 282 (log ε/2 3.84), 290 inflection (log ε/2 3.82). ν_{OH} ~2430 in Nujol; $\nu_{C=O}$ 1716, 1629 in $CHCl_3$, 1706, 1656 (weaker band), 1615 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $(C_{12}H_{11}NO_3)_2 \cdot C_6H_6$ (512.54): benzene, 15.24; C, 70.30; H, 5.51; N, 5.47. Found: wt. loss after 10 min. at 100°, 15.81; C, 70.22; H, 5.65; N, 5.64.

(b) 1-Maleylindoline, white, m.p. 155–156.5° dec. $\lambda_{max}^{95\%\ C_2H_5OH}$: 255 mμ (log ε 4.05), 283 (3.87), 292 inflection (3.84). ν_{OH} ~2440 in $CHCl_3$, ~2490 in KBr; $\nu_{C=O}$ 1710, 1625 in $CHCl_3$, 1701, 1651 (weaker band), 1611 cm.$^{-1}$ in KBr.

Anal. Calcd. for $C_{12}H_{11}NO_3$ (217.22): C, 66.35; H, 5.10; N, 6.45. Found: C, 66.34; H, 5.23; N, 6.44.

1-Succinylindoline. Indoline (2.38 g., 0.0200 mole) was added to a warm solution of succinic anhydride (2.00 g., 0.0200 mole) in benzene (35 cc.). The solution was cooled for 15 min., causing separation of white crystals (3.86 g., 0.0176 mole, 88%), m.p. 165–166.5°. Three recrystallizations from acetonitrile gave beautiful white needles, m.p. 167–168°. $\lambda_{max}^{95\%\ C_2H_5OH}$: 252 mμ (log ε 4.19), 281 (3.65), 290 (3.58). ν_{OH} ~2670; $\nu_{C=O}$ 1705, 1653 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{12}H_{13}NO_2$ (219.23): C, 65.74; H, 5.98; N, 6.29. Found: C, 65.85; H, 5.93; N, 6.50.

1-Maleyl-2-methylindoline. 2-Methylindoline (6.46 g., 0.0485 mole) was added slowly to a cold solution of maleic anhydride (4.47 g., 0.0456 mole) in benzene. The solution was stirred and cooled in ice for 5 min. and then the bright yellow crystals of 1-maleyl-2-methylindoline (8.57 g., 0.0371 mole, 81%), m.p. 112–113.5° dec. were filtered. One recrystallization from benzene yielded the analytical sample, m.p. 114–114.5° dec. $\lambda_{max}^{95\%\ C_2H_5OH}$: 250 mμ (log ε 4.04), 282 (3.75), 289 (3.74). ν_{OH} ~2240; $\nu_{C=O}$ 1704, 1623 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{13}H_{13}NO_3$ (231.24): C, 67.52; H, 5.67; N, 6.06. Found: C, 67.73; H, 5.65; N, 5.96.

Hydrolysis of 1-maleylindoline. 1-Maleylindoline (m.p. 155–156.5° dec., 5.61 g., 0.0258 mole) was added to aqueous 30% potassium hydroxide (43 cc.), causing the formation of a white gel, which dissolved upon heating, with the liberation of an oily layer of indoline. The mixture was refluxed for 3 hr., then cooled and extracted with ether. Evaporation of the ether left a residue of crude indoline (3.03 g., 0.0254 mole, 98%), which was converted in ether solution to the picrate (7.82 g., 0.0224 mole, 87%), m.p. 170–174° dec. One recrystallization from benzene gave yellow needles, m.p. 174–176° dec., mixed melting point with indoline picrate, 174–176° dec. The alkaline solution was neutralized slowly with hydrochloric acid. At a *p*H of about 8 a light violet powder precipitated, possibly monopotassium fumarate (0.44 g., 0.00285 mole, 11%), m.p. >300°, which did not contain nitrogen or halogen. The solution was then acidified to a *p*H of about 2 and extracted with ether in a liquid-liquid extractor for 2 days. Evaporation of the ether left a light brownish residue of fumaric acid (2.22 g., 0.0191 mole, 74%), which had an infrared spectrum in Nujol identical with that of an authentic sample.

Hydrolysis of 1-maleyl-2-methylindoline. 1-Maleyl-2-methyl-2-methylindoline (3.05 g., 0.0132 mole) was refluxed with aqueous 30% potassium hydroxide (50 cc.) for 3 hr. The reaction mixture was cooled, extracted with ether, and the picrate (4.29 g., 0.0118 mole, 89%), m.p. 157–159°, prepared directly from the ether solution. One recrystallization from benzene gave yellow needles, m.p. 159–160°, mixed m.p. 159–160° with 2-methylindoline picrate. The colorless alkaline solution was acidified to a *p*H of about 2 with 46% sulfuric acid and extracted with ether in a liquid-liquid extractor for 36 hr. Evaporation of the ether gave fumaric acid (1.21 g., 0.0104 mole, 79%), sublimes above 210°.

(2-Methyl-3-indole)succinic acid (IIb). (a) *From rearrangement of 2-methyl-3-(1-maleyl-2-indolinyl)indole (cis-*Ib, *maleyl indole:2-methylindole dimer).* 2-Methyl-3-(1-maleyl-2-indolinyl)indole[8] (9.35 g., 0.0270 mole) was refluxed with aqueous 30% potassium hydroxide (90 cc.) for 3 hr. The reaction mixture was cooled and extracted with ether to remove indole (2.75 g., 0.0235 mole, 87%), m.p. 50–51° after sublimation, mixed m.p. 50–52° with an authentic sample. The infrared spectra in Nujol of the two samples were identical. The alkaline solution was acidified to Congo Red with 46% sulfuric acid and extracted with ether in a liquid-liquid extractor for 2 days. Evaporation of the ether left a light yellowish solid (6.4 g., 0.0259 mole, 96%), m.p. 203–206° dec. Three recrystallizations from acetonitrile, with charcoal, yielded (2-methyl-3-indole)succinic acid as white crystals, m.p. 209–211° dec., mixed m.p. 209–212° dec. with an authentic sample[9,10] of m.p. 210–212° dec. The infrared spectra in Nujol of the two samples were identical.

(b) *From rearrangement of 2-methyl-3-(1-fumaryl-2-indolinyl)indole (trans-*Ib, *fumaryl indole:2-methylindole dimer).* 2-Methyl-3-(1-fumaryl-2-indolinyl)indole[8] (2.10 g., 0.00606 mole) was refluxed with aqueous 30% potassium hydroxide (50 cc.) for 18 hr. The reaction mixture was cooled and extracted with ether to remove indole (0.51 g., 0.00435 mole, 72%), m.p. 51–52° after sublimation. The alkaline solution was acidified to a *p*H of about 2 with 46% sulfuric acid and extracted with ether in a liquid-liquid extractor for 4 days. Evaporation of the ether left a nearly violet residue, which was recrystallized once, with charcoal, from acetonitrile, yielding (2-methyl-3-indole)succinic acid as white crystals (1.31 g., 0.00530 mole, 87%), m.p. 205–208° dec., mixed m.p. 205–209° dec., with an authentic sample[9,10] of m.p. 208–210° dec.

(c) *From rearrangement of 2-methyl-3-(1-maleyl-3-methyl-2-indolinyl)indole (cis-*Id, *maleyl skatole:2-methylindole dimer).* 2-Methyl-3-(1-maleyl-3-methyl-2-indolinyl)indole[8] (5.00 g.,

(16) S. Fujise, *Sci. Papers Inst. Phys. Chem. Research (Tokyo)*, **9**, 96 (1928).

(17) W. Leithe, *Monatsh. Chem.*, **52**, 161 (1929).

(18) J. W. Brühl, *Z. phys. Chem.*, **16**, 219 (1895).

(19) M. Wenzing, *Ann.*, **239**, 245 (1887).

(20) O. Carrasco, *Gazz. chim. ital.*, **38**, II, 306 (1908).

0.0139 mole) was refluxed with aqueous 30% potassium hydroxide (50 cc.) for 3 hr. The yellow color of the solid disappeared immediately. After about an hour, an oil was observed on top of the solution and steam distilling up into the condenser. At the end of the reflux period, the reaction mixture was cooled, causing the oil to solidify. Extraction with ether (3 × 50 cc.) removed skatole (1.73 g., 0.0132 mole, 95%), m.p. 89–92°. Sublimation gave a sample, m.p. 95–96°, mixed melting point with an authentic sample, 95–96°. The alkaline solution was acidified to a *p*H of about 2 with 46% sulfuric acid and extracted with ether in a liquid-liquid extractor for 4 days. Evaporation of the ether gave a light tan solid (3.44 g., 0.0139 mole, 100%), m.p. 203–206° dec. Recrystallization from acetonitrile gave (2-methyl-3-indole)succinic acid as a white powder (3.12 g., 0.0126 mole, 91%), m.p. 207.5–209° dec., mixed m.p. 208–210° dec. with an authentic sample[9,10] of m.p. 208–210° dec. The infrared spectra in Nujol of the two samples, after drying at 90°, were identical.

(d) *From rearrangement of spiro[(8-carboxy-10-methyl-6,7,8,9,9a,10 - hexahydrobenzo[b]pyrrocol - 6 - one) - 9,3′ - (2′-methyl[3]pseudoindole)] (rearrangement product of maleyl skatole:2-methylindole dimer).* The rearrangement product of maleyl skatole:2-methylindole dimer[8] (1.85 g., 0.00513 mole) was refluxed with aqueous 30% potassium hydroxide (25 cc.) for 13 hr. A white substance was observed steam distilling up into the condenser during the reflux period. The reaction mixture was cooled and extracted with ether (3 × 25 cc.), to remove skatole, m.p. 94–95°, which was purified by sublimation at 75° (12 mm.) (0.63 g., 0.0048 mole, 94%), m.p. 96°, and identified by mixed melting point and Nujol infrared comparison with an authentic sample. The aqueous solution was acidified to a *p*H of about 2 with 46% sulfuric acid and extracted with ether in a liquid-liquid extractor for 24 hr. Evaporation of the ether gave a white solid (1.35 g.), m.p. 198–205° dec. One recrystallization from acetonitrile gave (2-methyl-3-indole)succinic acid as a white powder (1.19 g., 0.00482 mole, 94%), m. p. 209–210.5° dec., mixed m.p. 208–210° dec. with an authentic sample[9,10] of m.p. 208–210° dec. The infrared spectra in Nujol of the two samples were identical.

(2-Phenyl-3-indole)succinic acid (IIc). (a) *From rearrangement of 2-phenyl-3-(1-maleyl-2-indolinyl)indole (cis-*Ic, *maleyl indole:2-phenylindole dimer).* 2-Phenyl-3-(1-maleyl-2-indolinyl)indole[8] (3.97 g., 0.00972 mole) was refluxed with aqueous 30% potassium hydroxide (50 cc.) for 3 hr. Indole sublimed into the condenser during the reflux period. The reaction mixture was cooled and extracted with ether to remove indole. Considerable material (3.08 g.) was insoluble in both the ether and aqueous alkaline layers. This was assumed to be largely the potassium salt of unchanged starting material. It was refluxed with fresh aqueous 30% potassium hydroxide (50 cc.) for an additional 4 hr. and then worked up in the same manner as the original reaction mixture. This time no water- and ether-insoluble material remained. The original aqueous layer was acidified to Congo Red with 46% sulfuric acid, the solution evaporated to dryness on a steam bath, and the residue extracted with ether in a Soxhlet extractor for a day. Evaporation of the ether left a light pink residue of (2-phenyl-3-indole) succinic acid, m.p. 255–258° dec.

The total yields of products were: indole (0.35 + 0.55 g., 0.00767 mole) 79%, m.p. 50–51° after sublimation, and (2-phenyl-3-indole)succinic acid (1.33 + 1.26 g., 0.00838 mole) 86%. Three recrystallizations from acetonitrile, with charcoal, yielded (2-phenyl-3-indole)succinic acid-acetonitrile complex as white crystals, m.p. 183.5–184.5°, mixed m.p. 183–184° with a sample of m.p. 183–184° prepared from 2-phenylindole and maleic acid. The infrared spectra in Nujol of the two samples were identical.

(b) *From 2-phenylindole and maleic acid.* By a modification of the method of Noland and Lange[9] for the preparation of (2-methyl-3-indole)succinic acid, a mixture of 2-phenylindole (1.47 g., 0.00761 mole) and maleic acid (0.88 g., 0.00757 mole) was heated at 140° in an oil bath for 15 min. The dark blue-green melt solidified upon cooling. The acid appeared to be unstable and did not crystallize well from ethanol-water, chloroform, or methylene chloride. From acetonitrile, however, two recrystallizations, with charcoal, gave white crystals (1.74 g., 0.00528 mole of the acid, 70%), m.p. 185–186°. Three additional recrystallizations from acetonitrile, followed by drying *in vacuo* at 90°, yielded (2-phenyl-3-indole)succinic acid as an acetonitrile complex in the form of white crystals, m.p. 189–190°. $\lambda_{max}^{95\%\ C_2H_5OH}$: 224 mμ (log ε/2 4.41), 234 inflection (log ε/2 4.35), 301 (log ε/2 4.22). ν_{NH} 3280 in KBr, 3310 in Nujol; ν_{OH} ~2600 in KBr and Nujol; $\nu_{C=O}$ 1682 in KBr, 1694 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $(C_{18}H_{15}NO_4)_2 \cdot CH_3CN$ (659.67): neut. equiv. 164.92; C, 69.18; H, 5.04; N, 6.37. Found: neut. equiv. 172; C, 68.93; H, 5.08; N, 6.40.

(2-Phenyl-3-indole)succinic anhydride (anhydride of IIc). A solution of (2-phenyl-3-indole)succinic acid acetonitrile complex (2.50 g., 0.00758 mole of the acid) in acetic anhydride (50 cc.) was set aside for 2.5 days. The solvent was removed below 70° by vacuum distillation and the black residue was dissolved in methylene chloride–petroleum ether (b.p. 60–68°). After being set aside in a refrigerator for a month, the solution contained dark brownish crystals (0.78 g., 0.00268 mole, 35%), m.p. 190–193°. Five recrystallizations from methylene chloride–petroleum ether (b.p. 60–68°) yielded (2-phenyl-3-indole)succinic anhydride as slightly pinkish white crystals, m.p. 194°. $\lambda_{max}^{95\%\ C_2H_5OH}$: 225 mμ (log ε 4.40), 232 inflection (4.37), 301 (4.25). ν_{NH} 3390; $\nu_{C=O}$ 1860, 1782 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{18}H_{13}NO_3$ (291.29): C, 74.21; H, 4.50; N, 4.81. Found: C, 73.96; H, 4.51; N, 4.61.

An attempt[21] to prepare (2-phenyl-3-indole)succinic anhydride directly by the reaction of 2-phenylindole and maleic anhydride in a manner comparable to that used successfully with 2-methylindole and 1,2-dimethylindole[10] gave less promising results. A mixture of 2-phenylindole (8.42 g.) and maleic anhydride (4.28 g.) was fused at 120–130° in an oil bath for 10 min. The vigorous reaction yielded as the only crystalline product about 20 mg. of (2-phenyl-3-indole)succinic anhydride, m.p. 192–194°, mixed melting point with the sample previously described, 192–194°. The rest of the product was a sticky blue-black tar.

2-Methyl-2-(2-methyl-3-indole)succinic acid (XI). (a) *From rearrangement of 2-methyl-3-(1-itaconyl-2-indolinyl)indole* (IX, *itaconyl indole:2-methylindole dimer*). 2-Methyl-3-(1-itaconyl-2-indolinyl)indole[8] (4.20 g., 0.0116 mole) was refluxed with aqueous 30% potassium hydroxide (100 cc.) for 25 hr. The reaction mixture was cooled and extracted with ether. Evaporation of the ether left a tan viscous oil (1.07 g.), which upon sublimation gave indole (0.72 g., 0.0061 mole, 53%), m.p. and mixed m.p. 51–52° with an authentic sample. The alkaline solution was acidified to a *p*H of about 2 with 46% sulfuric acid and extracted with ether in a liquid-liquid extractor for 24 hr. Evaporation of the ether gave a light orange solid (2.19 g., 0.00838 mole, 72%), m.p. 210–214° dec. Three recrystallizations from acetonitrile gave 2-methyl-2-(2-methyl-3-indole)succinic acid as white crystals, m.p. 223–224.5° dec., mixed melting point with the sample prepared as described in the following section, 222–224° dec. The infrared spectra in Nujol were identical. $\lambda_{max}^{95\%\ C_2H_5OH}$: 225 mμ (log ε 4.51), 282(3.85), 289 (3.80). ν_{NH} 3430; ν_{OH} 2650; $\nu_{C=O}$ 1691 cm.$^{-1}$ in Nujol.

(b) *From rearrangement of 2-methyl-3-(1-citraconyl-2-indolinyl)indole (cis-*X, *citraconyl indole:2-methylindole dimer).* 2-Methyl-3-(1-citraconyl-2-indolinyl)indole[8] (3.75 g., 0.0104 mole) was refluxed with aqueous 30% potassium hydroxide (50 cc.) for 50 hr. The reaction mixture was cooled and extracted with ether. Evaporation of the ether left a tan oil (1.76 g.), part of which sublimed during 72 hr. at 70° (0.2 mm.), yielding indole (0.99 g., 0.0084 mole, 81%), m.p. 50–51° and mixed melting point with an authentic sample,

(21) Experiment performed by Larry L. Schaleger.

51–52°. The tan residual oil (0.77 g.) did not yield a crystalline succinyl derivative. The alkaline solution was acidified to a *p*H of about 2 with 46% sulfuric acid and extracted with ether in a liquid-liquid extractor for 3.5 days. The product is only slightly soluble in ether and precipitates from refluxing ether as white crystals of high purity. Evaporation of the ether gave 2-methyl-2-(2-methyl-3-indole)succinic acid (1.00 g., 0.00383 mole, 37%), m.p. 219–220° dec. Two recrystallizations from acetonitrile gave white microcrystals, m.p. 223–224° dec., mixed melting point with the sample prepared as described in the preceding section, 222–224° dec. The infrared spectra in Nujol and the ultraviolet spectra were identical.

Anal. Found: neut. equiv. 141; C, 64.53; H, 6.17; N, 5.64.

2-Methyl-2-(2-methyl-3-indole)succinic anhydride (anhydride of XI). 2-Methyl-2-(2-methyl-3-indole)succinic acid (0.66 g., 0.00252 mole) and acetic anhydride (25 cc.) were mixed and set aside at room temperature under a nitrogen atmosphere for 3 days. Since part of the acid remained undissolved, the mixture was warmed on a steam bath for 1 hr. and then set aside for 2 days. Evaporation of the solvent at 73° in a rotary vacuum evaporator left a brown residue, which was dissolved in methylene chloride–petroleum ether (b.p. 60–68°) and set aside in the refrigerator for 3 days. The resulting brownish precipitate (0.31 g., 0.00127 mole, 50%), m.p. 139–141°, was recrystallized four times from methylene chloride-petroleum ether (b.p. 60–68°), yielding 2-methyl-2-(2-methyl-3-indole)succinic anhydride as whitish crystals, m.p. 144°. $\lambda_{max}^{95\%\ C_2H_5OH}$: 223 mμ (log ε 4.49), 282-(3.86), 289(3.80). ν_{NH} 3430, 3400 (doublet); $\nu_{C=O}$ 1846, 1821 (weak), 1770 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{14}H_{13}NO_3$ (243.25): C, 69.12; H, 5.39; N, 5.76. Found: C, 69.12; H, 5.34; N, 5.70.

(2-Methyl-3-skatyl)succinic anhydride (anhydride of XII) (with William C. Kuryla). 2-Methylindole (12.1 g., 0.0921 mole) and itaconic anhydride (11.2 g., 0.100 mole) were fused on a steam bath for 15 min. The resulting brownish red oil had solidified to a hard glassy mass after 4 days. Crystallization from benzene gave a pinkish white solid (19.42 g., 0.0800 mole, 87%), m.p. 130–134°. Treatment with charcoal and three recrystallizations from benzene yielded (2-methyl-3-skatyl)succinic anhydride as a white solid, m.p. 134–135°. $\lambda_{max}^{95\%\ C_2H_5OH}$: 227 mμ (log ε 4.52), 284(3.85), 291-(3.79). ν_{NH} 3450 in $CHCl_3$, 3390 in Nujol; $\nu_{C=O}$ 1854, 1773 in $CHCl_3$, 1848, 1765 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{14}H_{13}NO_3$ (243.25): C, 69.12; H, 5.39; N, 5.76. Found: C, 69.00; H, 5.58; N, 5.56.

(2-Methyl-3-skatyl)succinic acid (XIX) (with T. R. Rajagopalan[22]). (2-Methyl-3-skatyl)succinic anhydride (1.50 g., 0.00575 mole) was dissolved in a solution of potassium hydroxide (10.7 g.) in water (37 cc.), and the resulting solution was refluxed for 3.5 hr. The cooled solution was acidified to Congo Red with concd. hydrochloric acid, causing the solution to become turbid. Extraction with ether and evaporation of the ether gave a light brown oil, which solidified after 2 or 3 days at room temperature. The resulting white solid was dissolved in aqueous sodium bicarbonate, the solution was washed with ether, and the aqueous phase was acidified and extracted with ether as previously described. The solidified residue from evaporation of the ether was filtered with the aid of benzene and dried, yielding (2-methyl-3-skatyl)succinic acid as a white solid (1.10 g., 0.00421 mole, 73%), m.p. 149–151° dec. $\lambda_{max}^{95\%\ C_2H_5OH}$: 226 mμ (log ε 4.52), 282 (3.84), 290 (3.79). ν_{NH} 3380, 3340 (stronger band); ν_{OH} 2650; $\nu_{C=O}$ 1698 cm.$^{-1}$ in Nujol.

Anal. Calcd. for $C_{14}H_{15}NO_4$ (261.27): C, 64.36; H, 5.79; N, 5.36. Found: C, 64.19; H, 5.81; N, 5.34.

The acid was recovered unchanged after attempted decarboxylation at 200–210°. A gas, assumed to be steam resulting from anhydride formation, was evolved at temperatures between the melting point and 210°, but, after alkaline hydrolysis of the cooled melt, the acid was recovered unchanged in 95% yield, as shown by mixed melting point and Nujol infrared comparisons.

(3-Indole)succinic acid (IIa) *from rearrangement under homogeneous conditions of 3-(1-maleyl-2-indolinyl)indole (cis-*Ia, *maleyldiindole*). A solution of maleyldiindole[4,9,10] (10.0 g., 0.0301 mole) in ethanolic 30% potassium hydroxide (30 g. potassium hydroxide in 86 cc. 95% ethanol) was refluxed for 3 hr. The solution was green at first but turned to orange when heating was begun, then back to green after cooling at the end of the reflux period. The ethanol was removed by vacuum distillation, and some indole also codistilled. The residue was washed with ether to remove remaining indole, then acidified to a *p*H of about 2 with 46% sulfuric acid and extracted with ether in a liquid-liquid extractor for 5 days. Evaporation of the ether gave (3-indole)succinic acid as a light yellowish solid (4.97 g., 0.0213 mole, 71%), m.p. 197–198.5° dec. The product is obtained in a purer initial state than that resulting from hydrolysis under heterogeneous conditions with aqueous potassium hydroxide.

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[CONTRIBUTION FROM BATTELLE MEMORIAL INSTITUTE AND THE UNIVERSITY OF ALABAMA MEDICAL SCHOOL]

Synthesis of Some 5- and 6-Chloro, 5-Methyl, and 5,6,7-Trimethyl Derivatives of Tryptamine

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The preparation of 5-chloro-*N*,*N*-dimethyl-, 6-chloro-*N*,*N*-dimethyl-, and 6-chlorotryptamine from the corresponding ring-chlorinated indoles has been carried out. A nine-step synthesis of 5,6,7,*N*,*N*-pentamethyltryptamine from 3,4,5-trimethylacetophenone and the preparation of 5,*N*,*N*-trimethyltryptamine from 5-methylindole are discussed. These compounds were prepared for psychopharmacological evaluation.

In a previous communication,[3] we reported that 4-chloro-, 4-methyl-, 3-methyl-, and 3,4,5-trimethyl-β-phenethylamine, at a dose level of 25 mg./kg. (intramuscular), evoked a strong rage response in

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