dried ether extracts and two crystallizations of the residue from benzene gave 72 mg. (49%) of methyl 5-hydroxy-6-methyl-2-pyridineoctanoate, m.p. 125–126°. On mixing with methyl carpyrinate of m.p. 125–126° (prepared below), the m.p. was unchanged, and the two compounds had identical infrared and ultraviolet spectra.

Anal. Calcd. for $C_{15}H_{23}O_3N$: C, 67.9; H, 8.7. Found: C, 67.6; H, 8.7.

5-Hydroxy-6-methyl-2-pyridineoctanoic Acid (Carpyrinic Acid) (III).—A mixture of 45 mg. of the methyl ester, 2.5 ml. of water, 4 ml. of 95% ethanol and 410 mg. of potassium hydroxide was heated under reflux for 4 hr. and then the solution was concentrated to a gel by heating on the steam-bath under a nitrogen stream. After being acidified to *p*H 2 with hydrochloric acid, the solution was concentrated to dryness and the residue was digested repeatedly with dry acetone. Concentration of the acetone digests gave carpyrinic acid hydrochloride which was crystallized from dry acetone. It partially melted at 78–83°, resolidified and melted at 110°. A sample dried at 80° (0.2 mm.) for 22 hr. melted at 110–111° (reported[4] m.p. 85–86.5°) and synthetic material was identical with that derived from carpaine.

Anal. Calcd. for $C_{14}H_{22}O_3NCl$: C, 58.4; H, 7.7. Found: C, 58.5; H, 7.5.

Methyl Carpyrinate from Carpaine.—Carpamic acid hydrochloride,[3] suspended in methanol, was treated with excess ethereal diazomethane overnight. The solution was concentrated to a small volume, ether and water were added and the ether phase was separated and washed with aqueous carbonate solution. Evaporation of the ether left a quantitative yield of methyl carpamate as an oil. This material was dehydrogenated following the procedure previously described[4] with the addition of magnetic stirring in the dehydrogenation vessel. Hydrogen evolution ceased after five hours (2.5 moles of hydrogen evolved) and the reaction mixture was filtered hot. The catalyst was digested with benzene and cooling the combined filtrate and digests gave a 68% yield of methyl carpyrinate, m.p. 125–126°; $\lambda_{max.}^{EtOH}$ 288 (ϵ 6,010), 224 (ϵ 8,210), $\lambda_{min.}$ 246 (ϵ 740) mμ; in 0.01 *N* potassium hydroxide in ethanol, $\lambda_{max.}$ 310 (ϵ 6,460), 245 (ϵ 11,540), 211 (ϵ 13,210), $\lambda_{min.}$ 271 (ϵ 720), 224 (ϵ 4,530) mμ [reported[4] for ethyl carpyrinate, λ^{EtOH} 287 (ϵ 6,030), 247 (ϵ 563), 223 (ϵ 8,140), $\lambda^{KOH-EtOH}$ 310 (ϵ 6,170), 272 (ϵ 603), 247 (ϵ 10,000) mμ].

BERKELEY, CALIFORNIA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING, UNIVERSITY OF CALIFORNIA, BERKELEY]

The Mutarotation of Isocolchicine

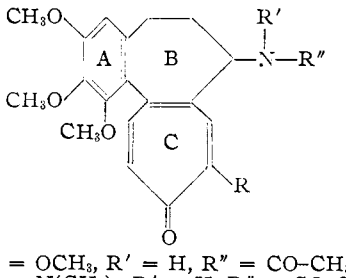
BY HENRY RAPOPORT AND JOE B. LAVIGNE[1]

RECEIVED NOVEMBER 10, 1955

Solutions of isocolchicine and some of its derivatives mutarotate in a number of non-polar solvents but not in ethanol. This phenomenon is not exhibited by colchicine and also disappears when the acetamido group is deacetylated or N-methylated. Crystallization of mutarotated isocolchicine restores the rotation to its initial value, and throughout the change the ultraviolet and infrared spectra remain constant. The reaction is first order with an activation energy of 23.7 kcal. Hypotheses involving solvent-complexing and change in state of aggregation in solution have been considered and discarded in favor of hindered rotation between rings A and C as the best explanation for mutarotation.

During work on the preparation of isocolchicine derivatives, it was decided to use the specific rotation of the starting isocolchicine as a reliable and rapidly determined criterion of purity. However, seemingly similar samples (based on m.p. behavior) gave considerably different specific rotations, and duplicate determinations on the same sample frequently differed widely. This lack of consistency finally was found to be due to a change in specific rotation with time. Since it was quite unexpected that isocolchicine solutions should mutarotate, a detailed investigation was made and forms the substance of this report. An independent and prior observation of this phenomenon with isocolchicine has been reported recently,[2] and it also has been observed to occur with methylthioisocolchicide.[3]

Generally, mutarotation has been the result of a structural change or, more frequently, the result of diastereomer formation in solution.[4] Another and quite different type is that observed in the reversible denaturation of proteins[5] in which mutarotation is caused by the change in state of aggregation of the species in solution. Presumably then any change slow enough to be followed polarimetrically of the species in solution—either intramolecular or intermolecular, or even interaction with the solvent—might be a cause of mutarotation. In examining the isocolchicine structure[6] (I) with its single asymmetric carbon atom, it certainly is not obvious how this molecule fits into these categories for mutarotation. Therefore, an explanation was sought in a detailed study of the various factors that might be involved.



I, R = OCH_3, R' = H, R'' = CO-CH_3
II, R = $N(CH_3)_2$, R' = H, R'' = CO-CH_3
III, R = $NHCH_3$, R' = H, R'' = CO-CH_3
IV, R = OCH_3, R' = H, R'' = H
V, R = OCH_3, R' = CH_3, R'' = CO-CH_3

It was first necessary to exclude possible extraneous factors. That a trace of acid in the solvent chloroform might be the cause was eliminated by

(1) Supported in part from a generous grant by Smith, Kline and French Laboratories.

(2) R. F. Raffauf, E. F. Bumbier and G. E. Ullyot, THIS JOURNAL, **76**, 1707 (1954).

(3) L. Velluz and G. Muller, *Bull. soc. chim. France*, 198 (1955).

(4) R. L. Shriner, R. Adams and C. S. Marvel in "Organic Chemistry," Vol. 1, edited by H. Gilman, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 305.

(5) R. B. Simpson and W. Kauzmann, THIS JOURNAL, **75**, 5139 (1953), and references therein.

(6) See H. Rapoport, A. R. Williams, J. E. Campion and D. E. Pack, *ibid.*, **76**, 3693 (1954), for a review of the evidence leading to general acceptance of this structure.

observing the same mutarotation when potassium carbonate or triethylamine was added to the chloroform. Also, the mutarotation was unaffected whether the solution was kept in the dark, or exposed to the light of the sodium lamp or the fluorescent lamp. An impurity in the isocolchicine was not the cause since on evaporation of the chloroform and crystallization of the residue from ethyl acetate, various fractions exhibited the same mutarotation pattern, and 99.7% of the isocolchicine could be recovered. A typical mutarotation curve is shown in Fig. 1. Elimination of these extraneous factors as contributory to the mutarotation indicated this phenomenon was an intrinsic property of the molecule, and further data were needed in order to present an explanation.

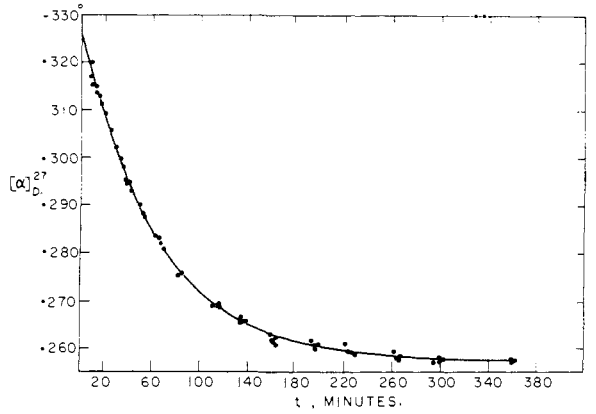


Fig. 1.—Mutarotation of isocolchicine in chloroform (c 1.01).

The fact that isocolchicine recovered from a mutarotated chloroform solution had the same specific rotation as it did initially rules out any permanent structural change in the molecule. However, to attain this full rotatory recovery, it was necessary to recrystallize from ethyl acetate or at least to heat with ethyl acetate and evaporate several times.[2] These observations indicate that a reversible change is involved and that the ethyl acetate treatment is necessary to obtain the oriented structure in the solid responsible for the initial rotation.

It has been observed previously[2] that no mutarotation takes place in ethanol. It does occur in all the relatively non-polar solvents tried,[7] *i.e.*, chloroform, methylchloroform, methylene chloride, bromoform and benzene. The initial and final rotations in these solvents, and the rate constants which will be discussed below, are given in Table I.

The structural requirements for mutarotation were sought, and the data obtained for the eight compounds examined are given in Table II. No mutarotation was observed with colchicine and two of its derivatives.[8] This may be due to an extremely rapid mutarotation or the absence of mutarotation. We are inclined toward the latter explanation since colchicine also showed no change in rotation at zero degrees. The methylamino and dimethylaminoisocolchicine derivatives, as well as isocolchicine itself, do mutarotate. However, both the hydrogen and the acetyl on the amino group of ring B are necessary, since the absence of either (compounds IV and V) is sufficient to eliminate mutarotation.

(7) The number of possible solvents is limited somewhat by the relative insolubility of isocolchicine.

(8) Structurally, these compounds are the same as the corresponding isocolchicine compounds, except that the position of the carbonyl and R groups in ring C are interchanged.

TABLE I

EFFECT OF SOLVENT ON THE MUTAROTATION OF ISOCOLCHICINE

Temp., °C.	Concn., %	Solvent	$k \times 10^5$, sec.$^{-1}$	[α]D, degrees Time, 0 [b]	Time, ∞
27	3.97	$CHCl_3$	24.9	−316	−269
27	1.02	$CHCl_3$	28.8	−328	−259
27	1.02	$CHCl_3$	26.5	−328	−257
25[a]	1.00	$CHCl_3$	23.9	−325	−257
28	0.49	$CHCl_3$	29.8	−331	−245
0	.50	$CHCl_3$	0.5	−329	−253
27	.026	CH_3CCl_3	6.9	−277	−228
27	.51	$CHBr_3$	19.3	−345	−258
28	.51	CH_2Cl_2	27.0	−300	−254
27	.069	C_6H_6	68.1	−318	−271

[a] Ref. 2. [b] Obtained by extrapolation.

Spectral examinations were made of mutarotating isocolchicine solutions in chloroform and methylene chloride in the hope of finding variations that might be correlated with a change in rotation. Both the infrared and ultraviolet spectra, however, were constant over a one-hour period whereas the half-life of mutarotation under these conditions is about 40 minutes.

That the mutarotation reaction was first order was shown by a plot of the log of the rotation at time t minus the final rotation *vs.* time.[9] In every case, this gave a straight line and two examples are given in Fig. 2. Further verification for a first-order reaction was found in the fact that changing the concentration from 0.5 to 4% caused very little change in the half-life of the reaction. The first-order rate constant was calculated from the slope of this line, and the values under various conditions are given in Tables I and II. From the rate constants for the mutarotation of isocolchicine in chloroform at 0 and 28°, the energy of activation was found to be 23.7 kcal.[9]

Any theory then that would explain the mutarotation must be consistent with the above facts—namely, (1) no permanent change takes place and crystallization from ethyl acetate returns the isocolchicine to its original rotation, (2) mutarotation occurs in various non-polar solvents but not in ethanol, (3) the isocolchicine-type structure is required in ring C as well as both a hydrogen and an acetyl group on the amino group of ring B, (4) the infrared and ultraviolet spectra remain unchanged, and (5) the mutarotation is a first-order reaction with an activation energy of 23.7 kcal.

A suggestion has been made[2] that the mutarotation may be the result of the formation of a stable complex between isocolchicine and the solvent chloroform. This seems unlikely in view of the fact that mutarotation is exhibited in a variety of solvents such as bromoform, methylene chloride, methylchloroform and benzene as well as in chloroform. Another argument against this theory was found in

(9) S. Glasstone, "Text-Book of Physical Chemistry," D. Van Nostrand Co., Inc., New York, N. Y., 1940, p. 1024.

TABLE II

THE SPECIFIC ROTATION OF SOME ISOCOLCHICINE AND COLCHICINE DERIVATIVES IN CHLOROFORM

Compound	Temp., °C.	Concn., %	$k \times 10^5$, sec.$^{-1}$	$[\alpha]_D$, degrees Time, O[a]	Time, ∞
Isocolchicine (I)	28	0.49	29.8	−331	−245
N,N-Dimethylaminoisocolchicide (II)	27	.39	37.6	−536	−300
N-Methylaminoisocolchicide (III)	27	.49	4.78	−370	−240
Desacetylisocolchicine[b] (IV)	27	1.00	...	−239	NC,[c] 5 hr.
N-Methylisocolchicine[d] (V)	28	0.99	...	−296	NC, 24 hr.
Colchicine	27	1.00	...	−134	NC, 96 hr.
Colchicine	0	0.65	...	−103	NC, 24 hr.
N,N-Dimethylaminocolchicide[e]	25	.50	...	−368	NC, 1.5 hr.
Methylthiocolchicide[f]	28	.94	...	−191	NC, 2.2 hr.

[a] Obtained by extrapolation. [b] R. F. Raffauf, A. L. Farren and G. E. Ullyot, THIS JOURNAL, **75**, 5292 (1953). [c] No change. [d] A. Uffer, O. Schindler, F. Santavy and T. Reichstein, *Helv. Chim. Acta*, **37**, 18 (1954). [e] Ref. 6. [f] H. Rapoport and J. B. Lavigne, THIS JOURNAL, **77**, 667 (1955).

the experiment in which aliquots were removed from a mutarotating solution at 6-, 20-, 50- and 100-minute intervals. These were very rapidly evaporated to dryness *in vacuo* at room temperature or below and in each case the residue retained one mole of chloroform per mole of isocolchicine. Reconstitution in chloroform gave solutions which mutarotated as if no interruption had occurred. Since the isocolchicine, both at the start of the reaction and after 80% completion, showed a constant one-to-one complex with the chloroform, it is unlikely that this complex formation is associated with the mutarotation.

An explanation that seemed attractive to us was one based on the degree of aggregation in solution. Since it is very probable that crystalline isocolchicine has a highly oriented polymeric structure linked through hydrogen bonds,[10] mutarotation might be due to dissociation of this structure in a manner analogous to that observed with proteins.[5] This hypothesis is consistent with the need for crystallization for a return to the initial rotational value. The necessity for a non-polar solvent might be explained by an extremely rapid dissociation in a polar solvent to an isocolchicine–solvent hydrogen-bonded complex and hence no observable mutarotation, as is the case in ethanol. The structural requirements are also consistent, since both a hydrogen and an acetyl group on the ring B-amino group would be needed for hydrogen bond, intermolecular interactions. Presumably other effects, such as possible intramolecular hydrogen bonding,[11] might be responsible for no observable mutarotation with colchicine.

Spectral constancy during mutarotation would be expected in the ultraviolet. In the infrared, this constancy eliminates the possibility of dissociation to a non-hydrogen bonded amide, since such a change would be easily distinguished.[12] However, this may be easily reconciled by postulating a dissociation from a higher polymer to a dimer, for example, and by breaking sufficient hydrogen bonds between nitrogen and oxygen to accommodate the energy of activation.

The crucial test for this dissociation postulate is a determination of the molecular weight as a function of time. When this was done cryoscopically in bromoform at 15° (under which conditions the half-life for mutarotation is about eight hours), the molecular weight remained relatively constant during a 10-hour period. The value found was that for the dimer, which is reasonable since the solution was 0.04 *M*. These data completely eliminate any dissociation hypothesis.

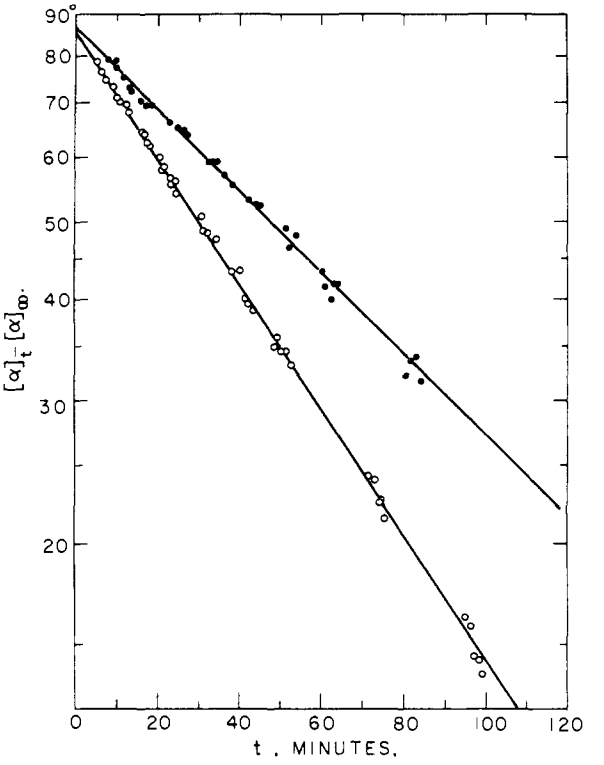


Fig. 2.—Mutarotation of isocolchicine in chloroform (O), (*c* 0.49) at 28° and in bromoform (●) (*c* 0.51) at 27°; log $([\alpha]_t - [\alpha]_\infty)$ *vs.* time.

Another proposal that might explain the mutarotation phenomenon was that of hindered rotation between rings A and C. If there is sufficient departure from coplanarity between these rings, a second source of asymmetry is introduced into the isocolchicine molecule, and mutarotation may be due to diastereomer formation as equilibrium between isomers is established in solution. This hypothesis is

(10) M. V. King, J. L. de Vries and R. Pepinsky, *Acta Cryst.*, **5**, 437 (1952), have found such a structure for colchicine.

(11) R. M. Horowitz and G. E. Ullyot, THIS JOURNAL, **74**, 587 (1952).

(12) W. Klemperer, M. W. Cronyn, A. H. Maki and G. C. Pimentel, *ibid.*, **76**, 5846 (1954).

clearly consistent with conditions 1, 4 and 5 enumerated above. Crystallization achieves the reconversion to the one diastereomer and the original rotation. The ultraviolet and infrared spectra might be expected to remain constant while such a change occurs in solution. Activation energies in the range of 20–30 kcal. have been found for the racemization of hindered biphenyls,[13] paralleling the 23.7 kcal. activation energy in the present case. Also, the requirements of a constant molecular weight and a constant (one-to-one) chloroform complex are easily met by this explanation.

Reconciliation of the other data with this hindered rotation hypothesis is not so obvious. The lack of mutarotation in ethanol might be explicable on the basis of solvation of the acetamido group. This would increase its effective size enough to increase the activation energy and lead to only one diastereomer in solution. Methylation of the nitrogen again might have this same effect, *i.e.*, prevent mutarotation because of the increased size of the N-methylacetamido group. Deacetylation might decrease the size of this group sufficiently to lower the activation energy and make mutarotation unobservable at room temperature. Also, deacetylation might so affect the crystal structure that there is no appreciable preference for the one isomer. The absence of mutarotation with colchicine might be due to greater rigidity in this molecule, which seems to be supported by a study of models, and hence a significantly higher activation energy. This consideration of the solvent and structural requirements for mutarotation does not seem either to support or oppose the hindered rotation hypothesis.

The most important facts that must be rationalized with the hindered rotation postulate are the ultraviolet spectral data, since departure from planarity would be expected to lead to decreased conjugation between rings and a decreased absorption. The ultraviolet data for the various compounds are given in Table III together with the calculated values for mere addition of the two chromophoric systems.

TABLE III

ULTRAVIOLET ABSORPTION DATA FOR ISOCOLCHICINE AND SOME RELATED TROPOLONES

Compound	Solvent	λmax, mμ	ε
Isocolchicine	Ethanol	343	18,600
Tropolone methyl ether[a] + 1,2,3-Trimethoxybenzene	Ethanol	317	7,200
Isocolchicine	Methylene chloride	338	16,800
Tropolone methyl ether[b] + 1,2,3-Trimethoxybenzene	Isoöctane Methylene chloride	320	4,600
γ-Phenyltropolone methyl ether[b]	Isoöctane	330	13,800
Tropolone methyl ether[b] + Benzene[c]	Isoöctane Cyclohexane	320	4,600

[a] W. Cook, R. A. Raphael and A. R. Somerville, *J. Chem. Soc.*, 503 (1951); T. Nozoe, M. Sato and K. Matsui, *Sci. Repts. Tohoku Univ.*, **37**, 211(1953). [b] W. E. Doering and L. H. Knox, THIS JOURNAL, **73**, 828 (1951). [c] R. A. Friedel and M. Orchin, "Ultraviolet Spectra of Aromatic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1951.

(13) G. H. Beaven, D. M. Hall, M. S. Lesslie and E. E. Turner, *J. Chem. Soc.*, 854 (1952).

For isocolchicine, there is a greatly enhanced extinction coefficient as compared to the sum of tropolone methyl ether and 1,2,3-trimethoxybenzene, indicating conjugation between rings A and C. However, it is still possible to have both this conjugative effect and sufficient departure from coplanarity to allow for asymmetry. It has been demonstrated clearly that coplanarity is not essential for conjugation and significant departures from coplanarity may be accompanied by only a slight loss in conjugation.[13,14] The conjugation effect between two such unsaturated systems has been shown to be proportional to the $\cos^2 \theta$, where θ is the angle through which one ring is twisted out of coplanarity with the other.[15–17]

Thus it is possible to retain most of the conjugative effect by having a small angle of twist[18] and at the same time cause enough departure from coplanarity[19] to acquire asymmetry. Such an explanation for isocolchicine would be aided greatly if a completely planar reference system were available, but even in the case of γ-phenyltropolone methyl ether there is no surety of coplanarity in solution. The ultraviolet data certainly are not inconsistent with the lack of coplanarity proposal.

Considering all the data, the best explanation for the mutarotation of isocolchicine appears to be found in hindered rotation between rings A and C. This leads to a molecule with two asymmetric centers, and mutarotation results from diastereomer formation in solution. This also implies that it may be possible to isolate diastereomeric forms with some isocolchicine derivatives.

Experimental[20]

Isocolchicine.—Colchiceine was methylated[11] with diazomethane and, to separate the isocolchicine from its mixture with colchicine, either selective acid hydrolysis or crystallization were employed rather than the previously reported[11,21] protracted chromatography on alumina. Since colchicine is more rapidly hydrolyzed than isocolchicine, the methylated mixture was subjected to the action of 0.2 *N* hydrochloric acid at 100° for one hour. Colchiceine was recovered in 66% yield, and isocolchicine was easily obtained from the non-acidic fraction in 31% yield by crystallization. Alternatively, it was found that crystallization of isocolchicine directly from the methylation mixture could be effected in 29% yield by seeding the ethyl acetate solution; m.p. 224–225°, $[\alpha]^{25}D$ −313° (*c* 1.01, ethanol) (reported m.p. 225–226°,[21] 221.5–222.5°[11]).

(14) D. M. Hall and E. E. Turner, *ibid.*, 1242 (1955).

(15) H. B. Klevens and J. R. Platt, THIS JOURNAL, **71**, 1714 (1949); J. Guy, *J. chim. phys.*, **46**, 469 (1949).

(16) M. J. S. Dewar, THIS JOURNAL, **74**, 3349 (1952).

(17) See especially the excellent summary of this effect in conjugated systems, including biphenyls, by E. A. Braude, *Experientia*, **11**, 457 (1955); E. A. Braude and W. F. Forbes, *J. Chem. Soc.*, 3776 (1955).

(18) It is interesting in this regard that in colchinol methyl ether, the corresponding compound in which ring C is aromatic and six-membered, no evidence for decreased conjugation and departure from coplanarity could be found [H. Rapoport, R. H. Allen and M. E. Cisney, THIS JOURNAL, **77**, 670 (1955)]. This might reasonably be explained by the smaller six-membered ring offering less hindrance than the seven.

(19) X-Ray studies (ref. 10) have found colchicine to be "nearly flat" in the crystal. Perhaps this slight deviation from flatness is consistent with the present proposals. No data are available for isocolchicine.

(20) All melting points are corrected and those above 200° were taken in evacuated capillaries; microanalyses were performed by the Microchemical Laboratory, University of California, Berkeley.

(21) M. Sorkin, *Helv. Chim. Acta*, **29**, 246 (1946).

N,N-Dimethylaminoisocolchicide.—A solution of isocolchicine (200 mg., 0.5 mmole) in 8 ml. of 2.7 *M* methanolic dimethylamine in a sealed tube was placed in an oil-bath at 96°. After 1.5 minutes, the bath temperature was raised to 165° over an 8.5-minute period and, after an additional 4 minutes, the tube was removed. The residue from evaporation of the solvent was dissolved in 10 ml. of benzene and extracted with three 10-ml. portions of 1 *N* hydrochloric acid. Alkalization of the combined aqueous extracts to *p*H 11, extraction with benzene, and concentration of the dried benzene extracts gave a residue which was dissolved in ethyl acetate, filtered through a column of alumina (8 g., Merck) and crystallized from benzene after removal of the ethyl acetate. Dimethylaminoisocolchicide was thus obtained in 75% yield (154 mg.), m.p. 199–200°, $[\alpha]^{26}D$ −315 (*c* 0.31, ethanol).

Anal. Calcd. for $C_{23}H_{28}O_5N_2$: C, 67.0; H, 6.8; N, 6.8; OCH_3, 22.6; equiv. wt., 413. Found: C, 66.8; H, 6.8; N, 6.5; OCH_3, 22.5; equiv. wt., 419.

N-Methylaminoisocolchicide.—Isocolchicine was treated with methanolic methylamine in the same manner as described above for the dimethylamino compound, except that the only heating was at 100° for 24 hours. The methylaminoisocolchicide was isolated by the same procedure as was used with the dimethylamino compound, substituting ethyl acetate for benzene in the extractions. Sublimation at 220–230° (10 μ) of the crystals obtained from benzene gave 58% of material melting at 292–293°, $[\alpha]^{26}D$ −349 (*c* 1.05, ethanol) [reported[22] m.p. 272–275°, $[\alpha]^{27}D$ −357° (chloroform)].

(22) A. Uffer, *Helv. Chim. Acta*, **35**, 2135 (1952).

Anal. Calcd. for $C_{22}H_{26}N_2O_5$: C, 66.3; H, 6.6; N, 7.0. Found: C, 66.2; H, 6.5; N, 6.8.

Solvation Experiments.—From a solution of isocolchicine in chloroform, aliquots were removed at 6-, 20-, 50- and 100-minute intervals and concentrated *in vacuo* at room temperature. Final concentration was done at 0.3 mm. pressure and in each case the residue contained one mole of chloroform per mole of isocolchicine. The residue was then reconstituted in chloroform and the mutarotation followed as before, assuming that mutarotation stopped 0.5 minute after concentration began due to the rapid decrease in temperature and removal of solvent. In each case the sample resumed its place on the mutarotation curve as expected, allowing for the time of concentration (0.5 min.) and the time of reconstitution (1 to 4 min.).

Molecular Weight Determinations.—Bromoform was purified by washing with concd. sulfuric acid, water and satd. sodium carbonate. It was dried over potassium carbonate, filtered, distilled at reduced pressure, and stored at 0°; b.p. 53–54° (26 mm.), d^{20}_4 2.8875, d^{27}_4 2.8700.

A sample of isocolchicine (110.0 mg.) in bromoform (20.3 g., 7 ml.) was prepared at 15° and kept at this temperature except when melting point determinations were made. The initial determination, made 15 minutes after solution of the isocolchicine, showed a depression of 0.095° when compared to the pure solvent. The final determination, made after ten hours, showed a melting point lowering of 0.110°. Using 14.4 as the cryoscopic constant for bromoform, this leads to a molecular weight of 821 initially and 709 finally (mol. wt. of isocolchicine, 399.4).

BERKELEY, CALIFORNIA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

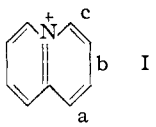
Aromatic Cyclodehydration. XXXI.[1] New Polycyclic Aromatic Systems Containing the Quinolizinium Nucleus

BY C. K. BRADSHER AND LEO E. BEAVERS[2,3]

RECEIVED NOVEMBER 18, 1955

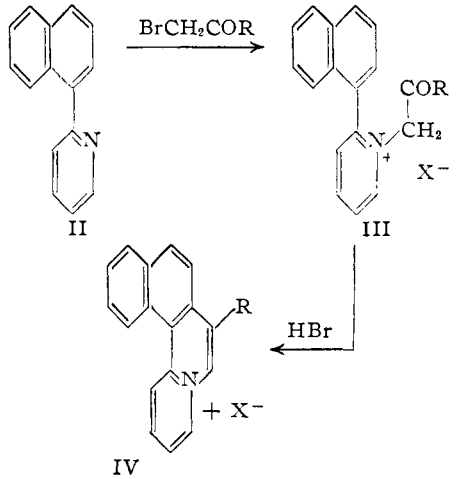
The two general methods described earlier for the synthesis of benzologs of the quinolizinium ion have both been applied to the preparation of some new tetra- and pentacyclic aromatic systems containing the quinolizinium nucleus. The systems include the naphtho[1,2-a]quinolizinium as well as the benzo[h]-, the benzo[j]- and the dibenzo[h,j]acridizinium ions.

Although it has been stated[4] that "the chemistry of polycyclic nitrogen heterocycles containing one hetero nitrogen atom has probably been the object of more intense investigation than any other single group in the broad field of heterocyclic chemistry," it was not until very recently that synthesis of the quinolizinium[5] ion I was first announced.[6] In the two most recent communications of this series, it was demonstrated how the methods of aromatic cyclodehydration could be extended to the synthesis of the first angular[7] (benzo[a]) and linear[1] (benzo[b]) benzologs of this aromatic nucleus. The present paper describes our effort to apply these two general methods to the synthesis of tetra- and pentacyclic aromatic systems containing the quinolizinium nucleus.



I

The literature lists no 2-(1-naphthyl)-pyridine (II), but our preparation, from 1-naphthyllithium and pyridine, afforded a picrate melting at a tem-



(1) For the preceding communication of this series, see THIS JOURNAL, **77**, 4812 (1955).

(2) Public Health Service Research Fellow of the National Institutes of Health, 1952–1954.

(3) Taken in part from a thesis submitted by Leo E. Beavers in partial fulfillment of the requirements for the degree of Doctor of Philosophy, 1955.

(4) R. C. Elderfield, "Heterocyclic Compounds," Vol. III, John Wiley and Sons, New York, N. Y., p. v.

(5) *Chemical Abstracts* nomenclature, *C. A.*, **46**, 13667 (1952).

(6) V. Boekelheide and W. G. Gall, THIS JOURNAL, **76**, 1832 (1954).

(7) C. K. Bradsher and L. E. Beavers, *ibid.*, **77**, 453 (1955).