During distillation, a small amount of crystals was often observed to condense in the receiver just prior to the collection of the nitro ester fraction. The crystals were removed, washed with ether and dried. The melting point (214–215°) was undepressed when mixed with an authentic sample of 2,3-dimethyl-2,3-dinitrobutane[5] (m. p. 215.5–216.0°).

Catalytic Reduction of 1-Nitro-1-methylethyl Ethyl Malonic Ester.—Twenty-seven and a half grams (0.10 mole) of 1-nitro-1-methylethyl ethyl malonic ester was reduced in a Parr hydrogenator using 3 g. of freshly prepared Raney nickel catalyst[6] and absolute ethanol (100 cc.) as a medium. The initial pressure was 50 lb.; 0.30 mole of hydrogen was taken up within forty-five minutes. After the hydrogenation was complete, considerable amounts of ammonia were evolved upon opening the pressure bottle. The catalyst was removed by filtration and most of the ethanol taken off on the steam-bath. Distillation of the liquid residue gave 13.0 g. (69%) of a nitrogen-free ester boiling at 206–210°. The b. p.'s recorded for ethyl malonic ester are 211°[7] and 207°.[8] Saponification gave the diacid, m. p. 111.0–111.5°; the m. p. of ethyl malonic acid is 111.5.[9]

5-(α-Nitro-α-methylethyl)-5-methylbarbituric Acid.—The barbituric acid was obtained by refluxing sodium ethoxide, nitro ester and urea (molar proportions 2:2:3) in absolute ethanol for three days. The solid salt which had precipitated was removed from the ethanol by filtration and dissolved in water. The aqueous solution was extracted with ether, filtered and finally acidified with concentrated hydrochloric acid. After standing in the cold overnight, the barbituric acid was removed by filtration, washed with water and recrystallized from 95% ethanol. The m. p. was 246.0–246.5°.

Anal. Calcd. for $C_8H_{11}O_5N_3$: N, 18.03. Found: N, 18.39.

Acknowledgment.—The authors wish to express their gratitude to the Commercial Solvents Corporation, who supplied the 2-chloro-2-nitropropane used in this investigation.

Summary

A series of 1-nitro-1-methylethyl alkyl malonic esters has been prepared by condensing 2-chloro-2-nitropropane with the sodium salt of the appropriate monoalkyl malonic ester.

Catalytic hydrogenation of a representative of the series, 1-nitro-1-methylethyl ethyl malonic ester, resulted in cleavage to ethyl malonic ester.

A typical member of the series, 1-nitro-1-methylethyl methyl malonic ester, has been converted to the corresponding barbituric acid.

HOLLAND, MICHIGAN RECEIVED NOVEMBER 7, 1949

(5) Seigle and Hass, *J. Org. Chem.*, **5**, 100 (1940).
(6) Pavlic and Adkins, THIS JOURNAL, **68**, 1471 (1946).
(7) Michael, *J. prakt. Chem.*, [2] **72**, 550 (1905).
(8) Conrad, *Ann.*, **204**, 134 (1880).
(9) Markownikow, *ibid.*, **182**, 332 (1876).

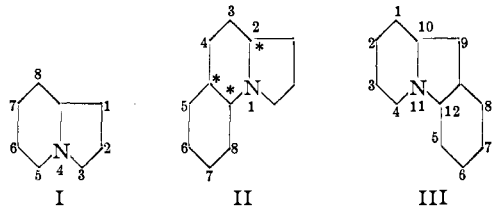
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Reductive Cyclization of Amino α-Keto Esters. A General Method for the Synthesis of Nitrogen-Heterocyclics Having Fused Five- and Six-Membered Rings

BY NELSON J. LEONARD AND JOSEPH H. BOYER[1]

A new general method has been devised for the synthesis of fully-saturated nitrogen-heterocyclics having fused five- and six-membered rings. The method makes possible especially the facile synthesis of certain polycyclic compounds containing the octahydropyrrocoline moiety (I). The octahydropyrrocoline nucleus (1-azabicyclo-[4.3.0]nonane) is of particular interest since it is common to a number of different alkaloids: a substituted octahydropyrrocoline constitutes the heterocyclic portion of the molecule in the tertiary bases of the *Solanum* and *Veratrum* alkaloid series[2]; 3-hydroxyoctahydropyrrocoline is a likely cyclic form of the alkaloid pelletierine[3]; a methyloctahydropyrrocoline portion has been suggested to be present in certain structural isomers of the lupin alkaloid, sparteine[4]; finally, the octahydropyrrocoline nucleus itself (also called δ-coniceine) has been obtained from the hemlock alkaloid, coniine.[5] Efficient methods for the synthesis of octahydropyrrocoline have not been lacking, but the present method is applicable also to the preparation of compounds of the type in which additional rings are fused through vicinal carbons of I, such as compounds II and VI.

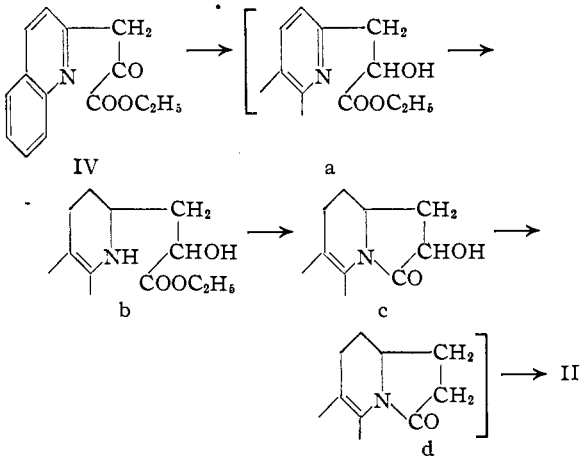
Isomeric with II and VI, a compound with structure III (11-azaperhydrofluorene) was re-



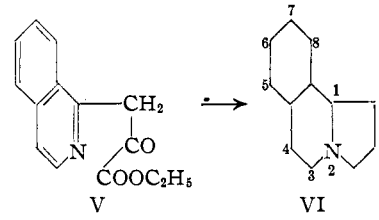
I II III

cently synthesized by Prelog, Frenkiel and Szpilfogel,[6] but by other means. The essential feature of the presently described method is the reductive cyclization of amino α-keto esters, which are available from the condensation of ethyl oxalate with compounds containing a methyl group activated by the imino linkage of a pyridinoid ring. The general method can be illustrated by the particular case of the synthesis of compound II, 1,2-trimethylenedecahydroquino-

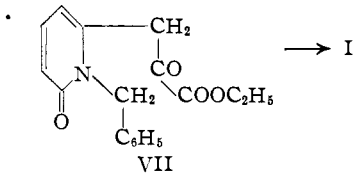
(1) Department of Chemistry, University of Michigan, Ann Arbor, Michigan.
(2) Uhle and Jacobs, *J. Biol. Chem.*, **160**, 243 (1945).
(3) Beets, *Rec. trav. chim.*, **62**, 553 (1943).
(4) Winterfeld and Nitzche, *Arch. Pharm.*, **278**, 393 (1940).
(5) Henry, "The Plant Alkaloids," Churchill Ltd., London, England, 4th edition, 1949, p. 20.
(6) Prelog, Frenkiel and Szpilfogel, *Helv. Chim. Acta*, **29**, 484 (1946).



line. Ethyl 2-quinolylpyruvate (IV) was prepared readily by condensation of ethyl oxalate with quinaldine in the presence of potassium ethoxide according to the directions of Borsche and Manteuffel,[7] in an application of the general Wislicenus method.[8] The substituted pyruvate (IV) was converted to 1,2-trimethylenedecahydroquinoline (II) by hydrogenation in dioxane solution over copper chromite catalyst at high temperature and pressure, conditions which have been shown in this Laboratory to effect reductive cyclization in the pyrrolizidine series.[9,10] It was unnecessary to isolate the intermediates in the conversion of IV to II, since the one-step reduction proceeded in satisfactory yield (*ca.* 60%), but in accordance with the generalizations for ease of hydrogenation and hydrogenolysis set forth by Adkins,[11] it appears that in so far as the reduction process takes place in a stepwise manner, the probable sequence of the steps is indicated in IVa, b, c, d. The composition of the final product (II) was established by analysis, molar refractivity and by analysis of the readily-obtained picrate and picrolonate derivatives. Although four racemates might be expected due to the asymmetric carbons in structure II, no attempt was made to establish their presence since the method apparently led to product predominant in one racemate. The oxime of ethyl 2-quinolylpyruvate (IV) was likewise converted to 1,2-trimethylenedecahydroquinoline (II) under the same reductive cyclization conditions, a conversion necessitating, at one stage, hydrogenolysis of a carbon–nitrogen rather than a carbon–oxygen bond. The closely related structural isomer of II, 1,2-trimethylenedecahydroisoquinoline (VI) was obtained in 66% yield by the reductive cyclization of ethyl 1-isoquinolylpyruvate (V). Again one racemate predominated in the reduction product, and its composition was established as in the case of II as $C_{12}H_{21}N$.



While it is difficult to conceive of logical structures—other than II and VI—for saturated tertiary bases of molecular formula $C_{12}H_{21}N$ which could result from the hydrogenation of the pyruvic esters IV and V, nevertheless it seemed desirable to verify the creation of the new five-membered ring in these and other examples. An excellent test would be found in the conversion of ethyl 2-pyridylpyruvate to octahydropyrrocoline (I), but this particular pyruvic ester is not readily obtainable by the general Wislicenus method. Instead, ethyl 1-benzyl-2-keto-1,2-dihydro-6-pyridylpyruvate (VII) was selected as the test compound since it could be prepared readily by ethyl oxalate condensation with 1-benzyl-6-methyl-2-pyridine, and since hydrogenolysis at the 1- and 2-positions of VII



would be expected to occur under the hydrogenation conditions employed and yet not interfere with the cyclization process. A five-membered ring was created during the hydrogenation of VII over copper chromite at high temperature and pressure, as established by the formation of octahydropyrrocoline (I), which was identified by comparison with authentic material.[12] With the creation of a new five-membered ring verified in this case, the structures of the more complicated ring compounds (such as II and VI) can be argued on analogical grounds in addition to the other evidence presented.

In applying the reductive cyclization method to ethyl 9-phenanthridylpyruvate (VIII) it was found advantageous to use the more active copper chromite catalyst prepared according to the directions of Riener[13] to obtain 9,10-trimethylene-

(7) Borsche and Manteuffel, *Ann.*, **526**, 22 (1938).

(8) Wislicenus and Kleisinger, *Ber.*, **42**, 1141 (1909).

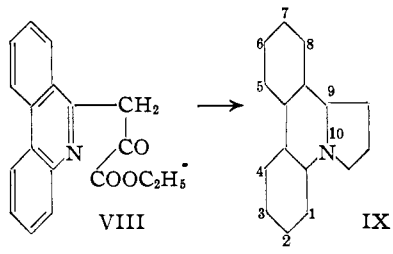
(9) Leonard and Burk, THIS JOURNAL, **72**, 2543 (1950).

(10) For leading reference, see Leonard and Felley, *ibid.*, **72**, 2537 (1950).

(11) Adkins, "Reactions of Hydrogen," University of Wisconsin Press, Madison, Wisconsin, 1937.

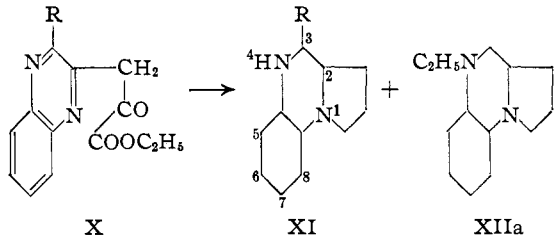
(12) The authors do not envisage this reaction (VII → I) as a useful method for the synthesis of octahydropyrrocoline, but only as a test of the formation of fused five- and six-membered rings under the hydrogenation conditions employed. The general concept of reductive cyclization has been employed satisfactorily in earlier-reported syntheses of the octahydropyrrocoline nucleus itself (*cf.* Tullock and McElvain, THIS JOURNAL, **61**, 961 (1939); Norton, Seibert, Benson and Bergstrom, *ibid.*, **68**, 1572 (1946); Beets and Wibaut, *Rec. trav. chim.*, **60**, 905 (1941); Boekelheide and Rothchild, THIS JOURNAL, **70**, 864 (1948)).

(13) Riener, *ibid.*, **71**, 1130 (1949).



VIII IX

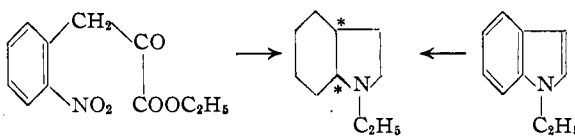
tetradecahydrophenanthridine (IX). Ring systems containing two nitrogen atoms were also prepared by the reductive cyclization process, as illustrated by the hydrogenation of ethyl 2-quinoxalylpyruvate (Xa) and ethyl 3-methyl-2-quinoxalylpyruvate (Xb). The product obtained



X XI XIIa

(a, R = H; b, R = CH_3)

from Xb by hydrogenation over copper chromite at high temperature and pressure had a composition consistent with structure XIb, 1,2-trimethylene-3-methyldecahydroquinoxaline, while the products obtained from Xa apparently included both 1,2-trimethylenedecahydroquinoxaline (XIa) and the N-ethylation product, 1,2-trimethylene-4-ethyldecahydroquinoxaline (XIIa). The reductive cyclization process was also shown to be applicable to pyruvic esters made by the condensation of ethyl oxalate with compounds containing a methyl group activated by a nitro group. For example, ethyl *o*-nitrophenylpyruvate (XIII), made by ethyl oxalate condensation with *o*-nitrotoluene, was converted to 1-ethyloctahydroindole (XIV) by reductive cyclization. Both racemic modifications of 1-ethyloctahydroindole (XIV) were obtained in the process, as



XIII XIV XV

indicated by their separation when the reduction product was subjected to chromatographic adsorption on alumina. Authentic samples of the two racemates of 1-ethyloctahydroindole were obtained for comparison by similar chromatography of the catalytic reduction product from 1-ethylindole. Direct comparison of derivatives of each of the two forms made possible the definite assignment of structure XIV to the two $C_{10}H_{19}N$ compounds. Apparently during the course of the reductive cyclization (XIII→XIV), the formation of a five-membered intermediate takes precedence over the formation of a six-membered ring, a behavior consistent with that encountered in other indole ring closures.[14]

Experimental

Preparation of Active Methyl Compounds

1-Benzyl-6-methyl-2-pyridone.—The procedure used was a modification of that employed by Binz and Räth[15] for the preparation of 1-benzyl-2-pyridone from 2-pyridone potassium. A mixture of 30 g. (0.23 mole) of 6-methyl-2-pyridone sodium, made by the Adams and Schrecker[16] modification of the Seide[17] method, 32 ml. (0.28 mole) of benzyl chloride and 125 ml. of absolute ethanol was refluxed for one hour. The precipitated sodium chloride was removed by filtration and, after concentration of the filtrate, additional sodium chloride was removed. The residual sirup was steam distilled, and the process was interrupted when the distillate no longer exhibited the odor of 2-benzoxy-6-methylpyridine. The undistilled residue was allowed to cool and to stand for twenty-four hours, during which time the product separated as colorless rectangular plates, m. p. 110–112°; yield 7.3 g. (16%). The infrared absorption spectrum exhibited a peak at 1645 cm.$^{-1}$, characteristic of an α-pyridone nucleus.[18]

Anal. Calcd. for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.61; H, 6.67; N, 7.25.

2-Benzoxy-6-methylpyridine.—The steam distillate obtained in the experiment described above was extracted thoroughly with ether, the ethereal solution was dried and the ether was removed. Fractional distillation of the residue *in vacuo* gave 23.5 g. (51%) of colorless liquid, b. p. 108–110° (1 mm.), which upon standing several days solidified in the form of colorless rectangular plates, m. p. 45–46°. The compound showed no infrared absorption peak at 1645 cm.$^{-1}$.

Anal. Calcd. for $C_{13}H_{13}NO$: C, 78.36; H, 6.58; N, 7.03. Found: C, 78.38; H, 6.75; N, 6.84.

1-Methylisoquinoline.—The authors are indebted to Dr. F. E. Cislak, Reilly Tar and Chemical Corporation, for a generous gift of this compound.

1-Methyl-3,4-dihydroisoquinoline. (a) **N-(β-Phenylethyl)-cyanoacetamide.**—The procedure of Naik and Bhat[19] for preparing cyanoacetanilide and N-(tolyl)-cyanoacetamide was used. A mixture of 22 g. (0.2 mole) of freshly distilled cyanoacetic ester and 24 g. (0.2 mole) of redistilled β-phenylethylamine was refluxed for twenty-four hours. Following cooling, the solid product was removed by filtration. Recrystallized from ethanol, the N-(β-phenylethyl)-cyanoacetamide was obtained as colorless plates, m. p. 93–95°; yield 27 g. (71%).

Anal. Calcd. for $C_{11}H_{12}N_2O$: C, 70.18; H, 6.43; N, 14.89. Found: C, 70.41; H, 6.26; N, 14.75.

(b) **Ring-Closure.**—Ring-closure of the amide to an isoquinoline derivative was effected by polyphosphoric acid, a reagent introduced for this general purpose by Snyder and Werber.[20] A mixture of 12 g. (0.07 mole) of N-(β-phenylethyl)-cyanoacetamide and 60 g. of polyphosphoric acid was heated with stirring at 170° for one and one-half hours. The reaction mixture was cooled and diluted with 120 ml. of water, and the aqueous solution was extracted with chloroform. Removal of the chloroform and distillation of the residue gave 2.1 g. (20%) of **1-methyl-3,4-dihydroisoquinoline**, b. p. 73–76° (1 mm.).

(14) Taylor and Baker, "Sidgwick's Organic Chemistry of Nitrogen," Oxford University Press, Oxford, England, 1937, p. 497.

(15) Binz and Räth, *Ann.*, **489**, 107 (1931).

(16) Adams and Schrecker, THIS JOURNAL, **71**, 1186 (1949).

(17) Seide, *J. Russ. Phys.-Chem. Soc.*, **50**, 534 (1918).

(18) The authors are indebted to Miss Elizabeth M. Petersen for determination of the infrared absorption spectra.

(19) Naik and Bhat, *J. Indian Chem. Soc.*, **4**, 547 (1927).

(20) Snyder and Werber, THIS JOURNAL, **72**, 2962 (1950).

Anal. Calcd. for $C_{10}H_{11}N$: N, 9.65. Found: N, 9.93.

The picrate, formed in ether and recrystallized from aqueous ethanol, was obtained as yellow needles, m. p. 193–194° (reported for 1-methyl-3,4-dihydroisoquinoline picrate 188–190°,[21] 193°[22]).

The hydrochloride, formed by passing dry hydrogen chloride into an ether solution of the base and recrystallized from acetone, was obtained as colorless plates, m. p. 196–197° (reported for 1-methyl-3,4-dihydroisoquinoline hydrochloride 196–198°[22]). Infrared analysis failed to show any peak at 2200 to 2260 cm.$^{-1}$, the region characteristic for nitrile absorption.[23]

Anal. Calcd. for $C_{10}H_{12}ClN$: C, 66.11; H, 6.66. Found: C, 66.15; H, 6.83.

2-Methyl-2-phenyl-1,2-dihydroquinoline.—In an attempt to prepare ethyl 2-quinolylacetate by the method which Woodward and Kornfeld[24] used for ethyl 2-pyridylacetate from 2-picolyllithium, addition of phenyllithium to the azomethine linkage of quinaldine occurred predominantly if not exclusively, with the formation of 2-methyl-2-phenyl-1,2-dihydroquinoline.[25] To a solution of phenyllithium prepared from 13.9 g. (2 atoms) of lithium in 800 ml. of anhydrous ether and 157 g. (1 mole) of bromobenzene, 143.2 g. (1 mole) of quinaldine was added and the reaction was carried out according to the directions cited. Fractionation of the product gave 100 g. of quinaldine and 31 g. (47% yield based upon unrecovered quinaldine) of a viscous oil, b. p. 185–190° (4–6 mm.). The oil crystallized upon standing in the refrigerator, and recrystallization from aqueous ethanol gave colorless hexagonal plates, m. p. 92–93°.

Anal. Calcd. for $C_{16}H_{15}N$: C, 86.84; H, 6.83; N, 6.33; mol. wt., 221. Found: C, 86.78; H, 6.16; N, 6.20; mol. wt., 222, 216 (Rast, camphor).

The picrate, formed in ether and recrystallized from aqueous ethanol, separated as green plates, m. p. 195–196°. (The properties of the picrate of 4-phenyl-2-methylquinoline are different.)

Anal. Calcd. for $C_{22}H_{18}N_4O_7$: C, 58.68; H, 4.03; N, 12.44. Found: C, 58.80; H, 3.96; N, 12.79.

The 3-nitrophthalamide, prepared by the general procedure of Alexander and McElvain,[26] was formed readily when 3-nitrophthalic anhydride and the amine were heated at 150–175° for ten to fifteen minutes. The oil crystallized on cooling and standing at room temperature and was recrystallized from aqueous ethanol, from which it separated as the hydrate in colorless prisms, m. p. 197–198°.

Anal. Calcd. for $C_{24}H_{18}N_2O_5 \cdot H_2O$: C, 66.65; H, 4.66; N, 6.48. Found: C, 66.48; H, 4.26; N, 6.44.

2-Methylquinoxaline.—The method employed was a modification of that used by Bennett and Willis[27] to prepare this compound from the isonitroso derivative of acetone. A solution of 21.6 g. (0.2 mole) of *o*-phenylenediamine and 14.4 g. (0.2 mole) of pyruvic aldehyde (Carbide and Carbon Chemicals Corporation) in 50 ml. of water and 50 ml. of ethanol was refluxed for thirty minutes. After removal of water and ethanol at atmospheric pressure, the residue was distilled *in vacuo*, b. p. 100–102° (1 mm.); yield 22.1 g. (77%).

2,3-Dimethylquinoxaline.[27]—This homolog was prepared in an analogous manner using 21.6 g. (0.2 mole) of *o*-phenylenediamine and 17.2 g. (0.2 mole) of biacetyl in 120 ml. of ethanol. The product was recrystallized from aqueous ethanol, m. p. 106°; yield 29.3 g. (91%).

9-Methylphenanthridine was prepared by the method of Morgan and Walls,[28] and **9-methylacridine**, by the method of Bernthsen[29] with the modifications of Porai-Koshits and Kharkharov.[30]

Preparation of the Pyruvic Esters

The procedure of Wislicenus,[8] as modified by Borsche and Manteuffel,[7] was employed. To a solution of 25 ml. of anhydrous ether and 18 ml. (0.3 mole) of absolute ethanol maintained under anhydrous conditions was added 4.0 g. (0.1 gram atom) of potassium at such a rate that the solution was kept at reflux. Following complete dissolution of the potassium, a solution of 7.5 g. (0.05 mole) of purified ethyl oxalate in 50 ml. of anhydrous ether was added dropwise and, after fifteen minutes, a solution of 0.05 mole of the active methyl compound in ether or ether–ethanol was added dropwise. In most cases the yellow condensation product began to appear within a few minutes. The reaction mixture was allowed to stand under anhydrous conditions for three to seven days. The precipitated solid was collected by rapid suction filtration and was immediately added to dilute acetic acid. The pyruvic ester separated completely within a few hours and was collected on a filter. All of the pyruvic esters were yellow or yellow-brown in color and crystallized as needles from aqueous ethanol. In Table I is found a description of the pyruvic esters prepared by this method.

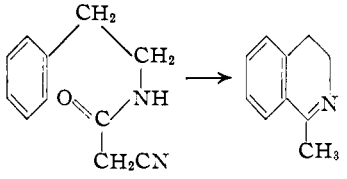
Ethyl 2-Quinolylpyruvate Oxime.—The oxime of ethyl 2-quinolylpyruvate, m. p. 164–165°, was made in 75% yield by the directions of Borsche and Manteuffel.[7]

Attempted Preparation of Ethyl 9-Acridylpyruvate.—The preparation was attempted in pyridine due to the low solubility of 9-methylacridine in ethanol and ether. Nine grams (0.1 mole) of potassium ethoxide, together with a trace of ethanol, was taken up in 40 ml. of anhydrous pyridine. Ethyl oxalate (0.05 mole) in pyridine and 9-methylacridine (0.05 mole) in pyridine were added, and the reaction mixture was allowed to stand three weeks. In another run the ethyl oxalate was omitted, but other quantities and conditions were kept the same. Both reaction mixtures were protected from moisture but *not* from air. At the end of three weeks, there was a deposit of 2.2 g. of an amorphous yellow powder in each reaction mixture. The two products were identical as indicated by their identical physical properties and the lack of any depression in the melting point of mixtures. It was thereby established that ethyl oxalate did not take part in the formation of this compound. The solid was insoluble in all of the usual solvents but could be recrystallized from ethyl oxalate, from which it separated as

(21) Späth, Berger and Kuntara, *Ber.*, **63**, 134 (1930).

(22) Whaley and Hartung, *J. Org. Chem.*, **14**, 650 (1949).

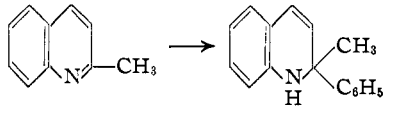
(23) The conversion of N-(β-phenylethyl)-cyanoacetamide to 1-methyl-3,4-dihydroisoquinoline by means of polyphosphoric acid



therefore involves steps of cyclization, hydrolysis and decarboxylation.

(24) Woodward and Kornfeld, private communication. Their preparation of ethyl 2-pyridylacetate has been submitted for publication in "Organic Syntheses."

(25) There is well-established precedent for such addition to the azomethine linkage



since Gilman and Gainer (THIS JOURNAL, **69**, 877 (1947)) have reported the addition of phenyllithium to quinoline to give 2-phenyl-1,2-dihydroquinoline and to 2-phenylquinoline to give 2,2-diphenyl-1,2-dihydroquinoline, and Gilman and Broadbent (*ibid.*, **70**, 280 (1948)) have reported the addition of butyllithium to 4-picoline to give 2-butyl-4-methylpyridine.

(26) Alexander and McElvain, *ibid.*, **60**, 2285 (1938).

(27) Bennett and Willis, *J. Chem. Soc.*, 1960 (1928).

(28) Morgan and Walls, *ibid.*, 2447 (1931).

(29) Bernthsen, *Ann.*, **224**, 1 (1884).

(30) Porai-Koshits and Kharkharov, *Bull. acad. sci. U. R. S. S., Classe sci. chim.*, 243 (1944).

TABLE I

SUBSTITUTED PYRUVIC ESTERS MADE BY CONDENSATION OF ETHYL OXALATE WITH ACTIVE METHYL COMPOUNDS

Active methyl compound	Pyruvic ester	Yield,[a] %	M. p., °C.	Molecular formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Quinaldine	Ethyl 2-quinolylpyruvate (IV)	52	132[7]	$C_{14}H_{13}NO_3$						
1-Methylisoquinoline	Ethyl 1-isoquinolylpyruvate (V)	52	192–194	$C_{14}H_{13}NO_3$	69.12	69.13	5.38	5.57	5.75	5.92
1-Benzyl-6-methyl-2-pyridone	Ethyl 1-benzyl-2-keto-1,2-dihydro-6-pyridylpyruvate (VII)	62	168–169	$C_{17}H_{17}NO_4$	68.21	68.20	5.73	5.86	4.68	4.71
9-Methylphenanthridine	Ethyl 9-phenanthridylpyruvate (VIII)	39	183–184	$C_{18}H_{15}NO_3$	73.70	73.50	5.16	5.26	4.78	4.79
2-Methylquinoxaline	Ethyl 2-quinoxalylpyruvate (Xa)	90	162[31]	$C_{13}H_{12}N_2O_3$						
2,3-Dimethylquinoxaline	Ethyl 3-methyl-2-quinoxalylpyruvate (Xb)	85	130[31]	$C_{14}H_{14}N_2O_3$						
o-Nitrotoluene	Ethyl *o*-nitrophenylpyruvate (XIII)[b]			$C_{11}H_{11}NO_5$						
Lepidine	Ethyl 4-quinolylpyruvate (XVI)	94	196[8]	$C_{14}H_{13}NO_3$						
9-Methylacridine	.....[c]									

[a] Based on active methyl compound. [b] Kindly supplied by Dr. L. E. Miller, University of Illinois. [c] See experimental.

TABLE II

REDUCTIVE CYCLIZATION OF THE PYRUVIC ESTERS

Pyruvic ester	Reduction product	Yield, %	B. p., °C.	Mm.	$n^{20}D$	d^{20}_4	Molecular formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	MR_D Calcd.[e]	MR_D Found
IV	1,2-Trimethylenedecahydroquinoline (II)[a]	60	65–66	1	1.5000	0.962	$C_{12}H_{21}N$	80.35	80.45	11.80	11.81	7.81	7.83	54.98	54.80
V	1,2-Trimethylenedecahydroisoquinoline (VI)	66	75–76	1	1.4960	0.950	$C_{12}H_{21}N$	80.35	80.48	11.80	11.98	7.81	7.71	54.98	55.11
VII	Octahydropyrrocoline (I)[12]	..	161	760											
VIII	9,10-Trimethylenetetradecahydrophenanthridine (IX)	40	114	0.5	1.5310	1.014	$C_{16}H_{27}N$	82.34	80.94	11.66	11.28	6.00	6.18	71.26	71.23
Xa	1,2-Trimethylenedecahydroquinoxaline (XIa)[b]	66	84–87	.5	1.5080	0.997	$C_{12}H_{24}N_2$	74.94	74.03	11.61	11.77	13.45	13.58	63.54	64.11
	1,2-Trimethylene-4-ethyldecahydroquinoxaline (XIIa)														
Xb	1,2-Trimethylene-3-methyldecahydroquinoxaline (XIb)	46	75	.5	1.5033	0.981	$C_{12}H_{22}N_2$	74.16	74.06	11.42	11.65	14.42	14.35	58.57	58.61
XIII	1-Ethyloctahydroindole (XIV)	..	40–42	.5	1.4780		$C_{10}H_{19}N$	78.36	78.22	12.50	12.35	9.14	9.50		

Reduction product	Picrate M. p., °C.	Picrate Carbon, % Calcd.	Picrate Carbon, % Found	Picrate Hydrogen, % Calcd.	Picrate Hydrogen, % Found	Picrate Nitrogen, % Calcd.	Picrate Nitrogen, % Found	Picrolonate M. p., °C.	Picrolonate Carbon, % Calcd.	Picrolonate Carbon, % Found	Picrolonate Hydrogen, % Calcd.	Picrolonate Hydrogen, % Found	Picrolonate Nitrogen, % Calcd.	Picrolonate Nitrogen, % Found
II	184–185	52.93	53.05	5.92	6.18	13.72	13.40	215–216	59.58	59.76	6.59	6.65	15.79	15.50
VI	212–214	52.93	53.22	5.92	6.16	13.72	13.86	209–210	59.58	59.67	6.59	6.71	15.79	16.15
I	226[c]													
IX	176–177	57.13	57.23	6.54	6.65	12.11	12.22	204–205	62.76	62.98	7.09	7.29	14.08	14.23
XIa								213–232	56.74	57.23	6.34	6.42	18.92	18.64
XIIa	260–263 (d.)[d]	45.05	45.08	4.54	4.70	16.81	16.33							
XIb	245–246[d]	44.17	44.01	4.33	4.46	17.17	17.12							
XIV	162–163	50.25	50.70	5.80	5.84	14.65	14.55							
	134–135	50.25	50.69	5.80	5.87	14.65	14.70							

[a] This compound was also obtained, in 40% yield, by the reductive cyclization of ethyl 2-quinolylpyruvate oxime. [b] Isolated only as the picrolonate. [c] No depression in melting point when mixed with an authentic sample[12] of octahydropyrrocoline picrate. [d] Dipicrate. [e] Values according to Shriner and Fuson, "Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., third edition, 1948, p. 45.

yellow needle-clusters, m. p. 358–360°. The infrared absorption spectrum indicated no peak at 1700 to 1740 cm.$^{-1}$ characteristic of an ester linkage, and the microanalysis confirmed the lack of oxygen in the product.

Anal. Calcd. for $C_{28}H_{20}N_2$: C, 87.47; H, 5.24; N, 7.29. Calcd. for $C_{28}H_{18}N_2$: C, 87.93; H, 4.74; N, 7.33. Found: C, 87.93; H, 5.02; N, 7.31.

(31) Borsche and Doeller, *Ann.*, **537**, 39 (1938).

On the basis of the physical properties and analysis, it is assumed that the product is 1,2-bis-(9-acridyl)-ethylene, $C_{28}H_{18}N_2$, and that it may result from the air oxidation of 9-methylacridine.[32]

Reduction of the Pyruvic Esters

All of the reductions were carried out in a steel reaction vessel under 200–300 atmospheres of hydrogen at a maximum temperature of 265°. Approximately 15 g. of copper chromite catalyst[33] and 100 ml. of dioxane were used per 0.1 mole of compound to be reduced. Catalyst prepared according to the directions of Riener[13] was found to decrease the reaction time 75% and to give better yields. In working up the reaction mixture, dioxane, water, and ethanol were removed by distillation through a ten-inch Fenske column at atmospheric pressure. With the exception of octahydropyrrocoline, b. p. 161° (760 mm.), the product was distilled at 0.5 to 2 mm. pressure. Picrate derivatives were prepared by the addition of the amine in ether to saturated picric acid in ether and were recrystallized from aqueous ethanol, from which all separated as bright yellow needles. Picrolonates were prepared in ether and recrystallized from aqueous ethanol. In Table II is recorded all pertinent information regarding the products of reductive cyclization and their derivatives.

Synthesis of 1-Ethyloctahydroindole (XIV).—Eight grams of 1-ethylindole (XV), prepared for us by Mr. Roy H. Bible according to the method of Fischer and Hess,[34] was hydrogenated over 8 g. of copper chromite catalyst[13] in 100 ml. of dioxane. Within one and one-half hours, the hydrogen pressure dropped from 3000 to 2400 lb. at 260°. The product was worked up in the usual way and the fraction boiling at 81–83° (20 mm.) was collected. A solution of 1 g. of the base in 150 ml. of petroleum ether (b. p. 40–60°) was chromatographed on a 15-g. column of activated alumina. One of the racemic modifications of 1-ethyloctahydroindole was not absorbed to an appreciable extent and was isolated as the picrate, m. p. 160–162°, from the first 150 ml. of petroleum ether which passed through the column. The other racemate was found in the first portion of the petroleum ether–benzene percolate and formed a picrate, m. p. 134–135°. Recrystallization of both picrates from aqueous ethanol gave yellow needles, one melting at 162–163°, the other at 134–135°. These derivatives were individually identical with the picrates, m. p. 162–163° and 134–135°, respectively, which were obtained by reductive cyclization of ethyl *o*-nitrophenylpyruvate followed by similar chromatography and picrate formation. All picrates had the correct analysis for $C_{10}H_{19}N \cdot C_6H_3N_3O_7$ (for representative values, see Table II), and no depression in melting point was observed on mixing the 162–163° picrates or on mixing the 134–135° picrates.

(32) The reaction is reminiscent of the air oxidation in alkaline medium of compounds of the chlorophyll type (Conant, Kamerling and Steele, THIS JOURNAL, **53**, 1615 (1931); Steele, *ibid.*, **53**, 3171 (1931)), and the product is similar in type to that obtained by the more vigorous selenium dioxide oxidation of lepidine (Kwartler and Lindwall, *ibid.*, **59**, 524 (1937)). Further work on this conversion is contemplated.

(33) "Organic Syntheses," **26**, 83 (1946).

(34) Fischer and Hess, *Ber.*, **17**, 559 (1884).

Summary

A general method has been devised for the synthesis of fully-saturated nitrogen-heterocyclics having fused five- and six-membered rings. The essential feature of the method is the reductive cyclization of amino α-keto esters. The ester intermediates are available from the condensation of ethyl oxalate with active methyl compounds in which the activating group is an imino or nitro function.

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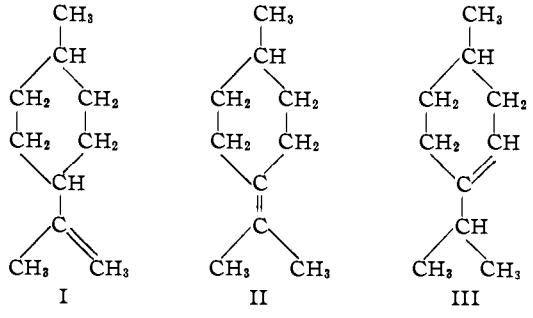
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Isomerization of 8(9)-*p*-Menthene[1,2]

BY ROBERT L. FRANK AND ROBERT E. BERRY

Many terpenes contain either the isopropenyl or the isopropylidene group. Examination of presumably pure samples of such compounds, whether of natural or synthetic origin, has often shown them to be mixtures of the isopropenyl and isopropylidene forms. The interrelationship between these two forms has been one of the perplexing problems encountered by terpene chemists.[3,4,5]

A prime consideration in the successful synthesis of terpenes having the isopropenyl group is the stability of this group under the conditions used in such syntheses. Herein is reported a study of the ease of rearrangement of pure 8(9)-*p*-menthene (I) to 4(8)- and 3-*p*-menthenes (II and III, respectively).



I II III

8(9)-*p*-Menthene (I) has previously been prepared by several means,[6,7,8] none of which, however, provided assurance that the product was not contaminated by the 4(8)-isomer. An unequivocal synthesis would appear to be the dehydration of 9-*p*-menthanol by some means which would not cause rearrangement of the double bond

(1) This is the fourth communication on the chemistry of terpenes. For the third, see THIS JOURNAL, **72**, 1645 (1950).

(2) Presented before the Organic Division of the American Chemical Society, Philadelphia, Pa., April, 1950.

(3) Simonsen, "The Terpenes," Cambridge University Press, 2nd edition, 1947, Vol. I, p. 2; *Endeavour*, **8** [29], 26 (1949).

(4) Thompson and Whiffen, *J. Chem. Soc.*, 1412 (1948).

(5) Escourrou, *Bull. soc. chim.*, **43**, 1204 (1928).

(6) Semmler and Rimpel, *Ber.*, **39**, 2584 (1906).

(7) Perkin and Pickles, *J. Chem. Soc.*, **87**, 650 (1905).

(8) Bogert, Hasseltrom and Firmenich, *Am. Perfumer*, **26**, 377 (1931).