oxide and 140 ml. of 50% alcohol was shaken with hydrogen at 25° and 50 p.s.i. on a Parr–Burgess apparatus. When the uptake of hydrogen had ceased (18 minutes), the catalyst was removed by filtration and to the filtrate was added 3.9 g. of redistilled *n*-butyraldehyde and 300 mg. of platinum oxide. The mixture was shaken with hydrogen at 45° and 50 p.s.i. until hydrogen uptake ceased (90 minutes). The mixture was filtered and the filtrate was mixed with 5 ml. of concentrated hydrochloric acid and evaporated *in vacuo*. Recrystallization of the residual paste from absolute alcohol–acetone gave a 70% yield of 2-diethylaminoethyl 4-butylamino-2-hydroxybenzoate dihydrochloride as tiny white prisms, m.p. 162–166°.

C.—A mixture of 13.0 g. of *pure* 3-(1-piperidyl)-propyl 4-amylamino-2-benzyloxybenzoate (*vide infra*), 2.0 g. of 7% palladium chloride on Darco G60 catalyst, 20 ml. of water, 12 ml. of concentrated hydrochloric acid and 120 ml. of alcohol was shaken with hydrogen at 45° and 50 p.s.i. until hydrogen uptake ceased (30 minutes). The catalyst was filtered off and the filtrate was treated with an excess of powdered sodium bicarbonate. The alcohol was removed *in vacuo*, the precipitated oil was taken up in benzene, and the benzene solution, after drying, was evaporated *in vacuo*. The residual 3-(1-piperidyl)-propyl 4-amylamino-2-hydroxybenzoate was then purified as in **A**, above.

The dialkylaminoalkyl 4-alkylamino-2-hydroxybenzoates prepared by the above methods are listed with their derivatives in Table V.

Dialkylaminoalkyl 4-Alkylamino-2-benzyloxybenzoates.—The dialkylaminoalkyl 4-amino-2-benzyloxybenzoates were reductively alkylated with an aldehyde, zinc dust and glacial acetic acid as described for ethyl 4-amino-2-benzyloxybenzoate above. The bases were purified by the method described for the corresponding 2-hydroxy bases above (the crude bases could not be catalytically debenzylated due to catalyst poisoning) and characterized as the flavianates. These are listed in Table VI.

The reaction between 2-benzyloxy-4-butylaminobenzoyl chloride (prepared *in situ* from the acid, pyridine and thionyl chloride at 10°) and a dialkylaminoalkanol gave 30–40% crude yields of the desired products. The compounds when prepared in this manner proved very difficult to purify, and the method was not as desirable as that described above.

3-Diethylaminopropyl 4-Aminobenzoate Phosphate.—The 4-amino base was prepared as previously described[14] and converted into the phosphate in absolute alcoholic solution. The product crystallized from alcohol in white needles, m.p. 215.5–217.5°.

Anal. Calcd. for $C_{14}H_{25}N_2O_6P$: N, 8.04; H_3PO_4, 28.14. Found: N, 7.88; H_3PO_4, 27.81.

The picrate formed yellow prisms from alcohol, m.p. 147.0–148.4°.

Anal. Calcd. for $C_{20}H_{25}N_5O_9$: N,[12] 5.84. Found: N,[12] 5.87.

3-(1-Piperidyl)-propyl 4-Butylaminobenzoate.—The reduction of 3-(1-piperidyl)-propyl 4-nitrobenzoate hydrochloride, m.p. 212.0–212.6° (lit.[15] m.p. 206–208°) to the 4-amino base[15] was carried out by means of iron and hydrochloric acid. **The phosphate** crystallized from alcohol in white prisms, m.p. 191.2–192.3°.

Anal. Calcd. for $C_{15}H_{25}N_2O_6P$: N, 7.77; H_3PO_4, 27.20. Found: N, 7.82; H_3PO_4, 27.20.

The picrate had m.p. 178.8–180.2°.

Anal. Calcd. for $C_{21}H_{25}N_5O_9$: N,[12] 5.70. Found: N,[12] 5.68.

Reductive alkylation with zinc dust, acetic acid and *n*-butyraldehyde (*vide supra*) gave the 4-butylamino base in high yield. **The monohydrochloride** crystallized from absolute alcohol in white prisms, m.p. 179.6–181.7°.

Anal. Calcd. for $C_{19}H_{31}ClN_2O_2$: N, 7.87; Cl, 9.99. Found: N, 7.74; Cl, 9.95.

The flavianate crystallized from dilute alcohol in orange needles, m.p. 185.4–186.4°.

Anal. Calcd. for $C_{29}H_{36}N_4O_{10}S$: S, 5.07. Found: S, 5.01.

2-Diethylaminoethyl 2-Benzyloxybenzoate.—The Hörenstein–Pählicke reaction between 2-benzyloxybenzoic acid[6] and 2-diethylaminoethyl chloride in isopropyl alcohol gave a high yield of the **hydrochloride**, rosettes of white needles from isopropyl alcohol, m.p. 109.0–110.3°.

Anal. Calcd. for $C_{20}H_{26}ClNO_3$: C, 66.01; H, 7.20; Cl, 9.74. Found: C, 66.24; H, 7.45; Cl, 9.81.

The picrate crystallized from absolute alcohol in rosettes of cottony yellow needles, m.p. 122.8–123.6°.

Anal. Calcd. for $C_{26}H_{28}N_4O_{10}$: N,[12] 2.52; N,[11] 7.56. Found: N,[12] 2.65; N,[11] 7.70.

3-Diethylaminopropyl 2-benzyloxybenzoate hydrochloride, prepared as above, crystallized from isopropyl alcohol in hygroscopic white needles, m.p. 105.4–106.5°.

Anal. Calcd. for $C_{21}H_{28}ClNO_3$: C, 66.74; H, 7.47; Cl, 9.38. Found: C, 66.75; H, 7.28; Cl, 9.23.

The picrate formed yellow needles from absolute alcohol, m.p. 102.6–103.6°.

Anal. Calcd. for $C_{27}H_{30}N_4O_{10}$: N,[12] 2.46; N,[11] 7.38. Found: N,[12] 2.56; N,[11] 7.52.

(14) Kamm, *ibid.*, **42**, 1031 (1920); v. Braun, Braunsdorf and Rath, *Ber.*, **55**, 1672 (1922).

(15) Barnes and Adams, THIS JOURNAL, **49**, 1313 (1927); Brill, *ibid.*, **54**, 2484 (1932).

RENSSELAER, N. Y. RECEIVED DECEMBER 13, 1950

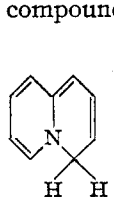
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ROCHESTER]

A Study of Some Quinolizone Derivatives

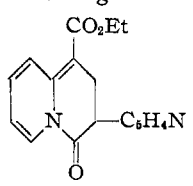
BY V. BOEKELHEIDE AND J. P. LODGE, JR.[1]

The condensation of ethyl 2-pyridylacetate and diethyl ethoxymethylenemalonate has been found to be a convenient reaction for the preparation of quinolizone derivatives. By hydrolysis and decarboxylation, the initial condensation product, 1,3-dicarbethoxy-4-quinolizone, was converted to either 1-carbethoxy-4-quinolizone or 4-quinolizone itself. Incidental to the establishment of structure of 1-carbethoxy-4-quinolizone, a new synthesis of *d,l*-lupinine was accomplished.

As part of a general study of quinolizine (I) and related compounds, we have investigated the use of ethyl 2-pyridylacetate as starting material for their synthesis. In view of previous successful utilizations of the condensation of ethyl 2-pyridylacetate and ethyl orthoformate for preparing II, an intermediate in the synthesis of *d,l*-sparteine,[2,3,4,5] it



I



II

(1) Sherman Clarke Fellow, 1949–1950.

(2) G. R. Clemo, W. McG. Morgan and R. Raper, *J. Chem. Soc.*, 1025 (1936); G. R. Clemo, R. Raper and W. S. Short, *ibid.*, 663 (1949).

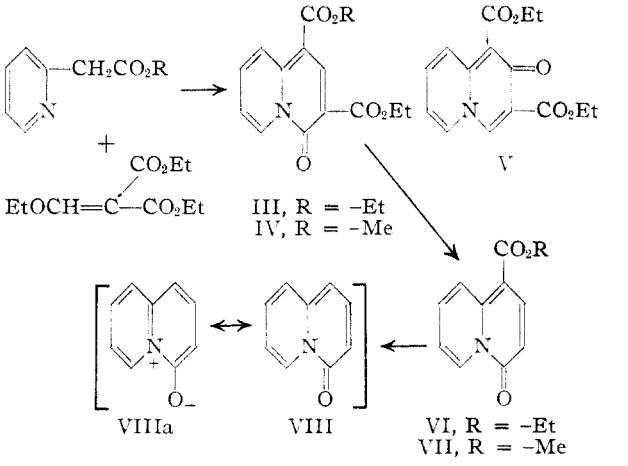
(3) N. J. Leonard and R. E. Beyler, THIS JOURNAL, **70**, 2298 (1948); **72**, 1316 (1950).

(4) F. Galinovsky and G. Kainz, *Monatsh.*, **77**, 137 (1947).

(5) F. Sorm and B. Keil, *Coll. Czechoslov. Chem. Commun.*, **13**, 544 (1948).

appeared probable that ethyl 2-pyridylacetate would likewise undergo cyclic condensation with suitable enol ethers. This proved to be correct for, when ethyl 2-pyridylacetate was heated with diethyl ethoxymethylenemalonate, a smooth reaction occurred yielding a product of composition $C_{15}H_{15}NO_5$ in 50% yield.

Since analogy could be found in the literature for predicting either III[6] or V[7] as the structure of the condensation product, it was necessary to distinguish between these two possibilities. This was done by subjecting the condensation product to hydrolysis and decarboxylation, whereupon there was formed a yellow solid whose melting point was in agreement with that reported by Späth and Galinovsky for the dehydrogenation product of 4-quinolizidone.[8] That the hydrolysis product was actually 4-quinolizone (VIII) rather than the 2-isomer was clearly shown by its conversion on catalytic reduction to 4-quinolizidone hydrochloride which was identical with an authentic specimen. Thus, the original condensation product must have structure III.



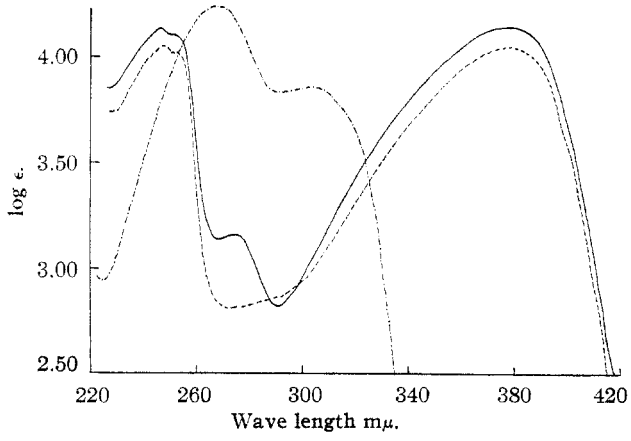
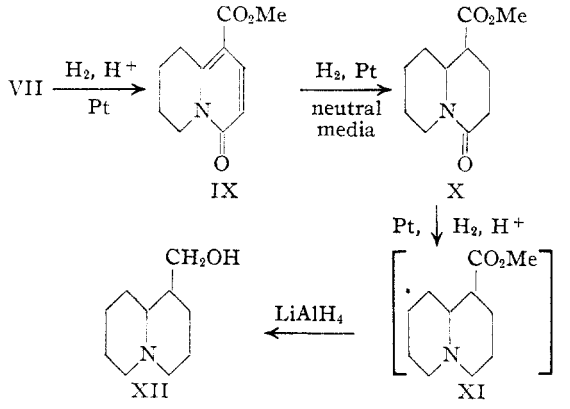


Fig. 1.—Ultraviolet absorption spectra in ethanol of 4-quinolizone (—), 4-quinolizone hydrochloride (- - - -) and 1-carbomethoxy-6,7,8,9-tetrahydro-4-quinolizone (- · - ·).

4-Quinolizone proved to be a water-soluble yellow solid, which gave bluish fluorescent solutions in ethanol, ether, benzene or strong acid. It gave a dark brown solution with ferric chloride reagent and formed crystalline salts with picric and hydrochloric acids. This behavior would indicate that ionic structures, such as VIIIa, make important contributions to the resonance hybrid. Such a conclusion is also consistent with its ultraviolet absorption spectrum as shown in Fig. 1.

Unfortunately, attempts to convert 4-quinolizone to 4-quinolizine (I) were unsuccessful. Both lithium aluminum hydride and *n*-butylmagnesium bromide formed colored complexes with 4-quinolizone, but on hydrolysis the 4-quinolizone was recovered unchanged. Also, the conversion of 4-quinolizone to 4-thioquinolizone followed by treatment with Raney nickel did not prove satisfactory. In this case the only product identified from the reaction mixture was α-picoline.

In carrying out the hydrolysis and decarboxylation of 1,3-dicarbethoxy-4-quinolizone, it was observed that the use of dilute acid with shorter reaction times led to the removal of only one carbethoxyl group. Although it would be expected that the carbethoxyl group adjacent to the amide linkage should be lost preferentially, evidence for this



was sought by repeating the reaction sequence with methyl 2-pyridylacetate instead of the corresponding ethyl ester. In this case, when the condensation product (IV) was subjected to dilute acid hydrolysis, it was found that loss of a carbethoxyl group, rather than a carbomethoxyl, occurred. Thus, if one disregards the possibility of a specific transesterification, the resulting carbomethoxy-4-quinolizone must have structure VII and, by inference, the previous hydrolysis product was VI.

In view of the close relationship of 1-carbomethoxy-4-quinolizone (VII) to lupinine, it seemed of interest to conclusively establish the structure of VII by its conversion to the racemic form of the alkaloid. This was accomplished by the series of hydrogenation steps shown below. The identity of the *d,l*-lupinine, obtained in our preparation, was demonstrated by the agreement of its melting point and those of its methiodide, picrolonate and picrate with the values recorded for *d,l*-lupinine by Clemo, Morgan and Raper.[9,10]

(6) E. Oshiai and Y. Ito, *Ber.*, **74**, 1111 (1941).

(7) R. B. Woodward and W. M. McLamore, THIS JOURNAL, **71**, 379 (1949).

(8) E. Späth and F. Galinovsky, *Ber.*, **69**, 761 (1936).

(9) G. R. Clemo, W. McG. Morgan and R. Raper, *J. Chem. Soc.*, 965 (1937); *ibid.*, 1574 (1938).

(10) The value of 179° given by Winterfeld and Cosel (*Arch. Pharm.*, **278**, 70 (1940)) for the melting point of *d,l*-lupinine picrolonate is not in agreement with that recorded by Clemo (203°) or our own result (203–204°).

It was somewhat surprising that the reduction of VII stopped at the tetrahydro stage in acid solution and only proceeded further when a neutral medium was employed. On the basis of its absorption spectrum (see Fig. 1), the tetrahydro derivative has been assigned structure IX.

Although two diastereoisomers are possible for XII, it would be expected that our method of reduction using Adams catalyst would yield only the *cis* isomer. The fact that we obtained a homogeneous product corresponding to *d,l*-lupinine, rather than *d,l*-isolupinine, supports the previous assignment of configuration made by Winterfield and Holschneider.[11]

Experimental[12]

1,3-Dicarbethoxy-4-quinolizone (III).—In a typical run, a mixture of 16.5 g. of ethyl 2-pyridylacetate[13] and 23.8 g. of diethyl ethoxymethylenemalonate[14] was heated in a distilling flask at 180° for eight hours. During this time approximately two molar equivalents of ethanol distilled. The residue was then taken up in a minimum amount of hot acetone and the solution was allowed to cool. From the solution there separated 15.0 g. (52%) of brown crystals, m.p. 123–129°, which on recrystallization from acetone or vacuum sublimation yielded pure yellow needles, m.p. 131–132°.

1,3-Dicarbethoxy-4-quinolizone dissolved in organic solvents or strong hydrochloric acid to give solutions having a blue fluorescence. It gave no color with ferric chloride reagent and did not form a picrate.

Anal. Calcd. for $C_{15}H_{15}NO_5$: C, 62.27; H, 5.23. Found: C, 62.31; H, 5.34.

4-Quinolizone (VIII).—A solution of 6.00 g. of III in 150 ml. of concentrated hydrochloric was boiled under reflux for one hour. The solution was then neutralized in the cold with solid potassium carbonate, and the mixture was repeatedly extracted with benzene until the benzene layer no longer became colored. After removal of the benzene under reduced pressure, the residual crystalline mass was sublimed at 80° under 2 mm. pressure. There resulted 2.45 g. (82%) of thick yellow crystals, m.p. 71–72° (lit.[8] gives m.p. 72–73°).

4-Quinolizone was strongly deliquescent and very soluble in water and the usual organic solvents, giving solutions having a blue fluorescence. It gave a dark brown solution with ferric chloride, and in benzene it gave a picrate, m.p. 136–137° (lit.[8] gives m.p. 136–137°), and a hydrochloride, m.p. 135–140°. The picrate and hydrochloride were deliquescent and too unstable for analysis. The infrared absorption spectrum of 4-quinolizone showed a very strong band at 6.0 μ as would be expected for a di-N-substituted amide.[15]

Anal. Calcd. for C_9H_7NO: C, 74.46; H, 4.86. Found: C, 74.42; H, 4.68.

When attempts were made to bring about reaction between 4-quinolizone and either lithium aluminum hydride or *n*-butylmagnesium bromide, orange-colored complexes formed but, even after several hours of heating of the reaction mixture, we were unable to isolate anything but starting material on hydrolysis.

Reduction of 4-Quinolizone.—A solution containing 490 mg. of 4-quinolizone, 100 mg. of prereduced Adams catalyst, 0.8 ml. of concd. hydrochloric acid and 15 ml. of ethanol was subjected to hydrogenation at room temperature under an atmospheric pressure of hydrogen. Four molar equivalents of hydrogen were absorbed in 2.5 hours and, after removal of the catalyst and solvent, there remained 620 mg. (97%) of crude crystalline hydrochloride, m.p. 131–138°. The crude product was recrystallized several times from ethyl acetate and yielded white needles, m.p. 138–140° (softening at 135°). Admixture of an authentic sample of 4-quinolizidone hydrochloride[16] gave no depression of melting point.

4-Thioquinolizone.—A mixture of 1.10 g. of 4-quinolizone and 0.49 g. of phosphorus pentasulfide was heated for one-half hour in a sublimation apparatus at 150°. The pressure was then reduced to 4 mm. and 4-thioquinolizone was collected on the cold finger. After two more sublimations, there was obtained 0.70 g. (57%) of deep yellow crystals, m.p. 98–100°.

Anal. Calcd. for C_9H_7NS: C, 67.05; H, 4.38. Found: C, 67.39; H, 4.57.

Attempted Hydrogenolysis of 4-Thioquinolizone.—A mixture of 5.0 g. of 4-thioquinolizone, 20 g. of Raney nickel catalyst and 200 ml. of ethanol was boiled under reflux for four hours. The catalyst was separated and the solvent was removed *in vacuo*. Distillation of the residue under a nitrogen atmosphere gave 100 mg. of oil boiling at 100–130° and about 100 mg. of additional oil boiling up to 200°. The lower boiling oil gave a yellow picrate, m.p. 158–160°, which showed no depression of melting point on admixture of authentic α-picoline picrate. The higher boiling oil was not identified.

1-Carbethoxy-4-quinolizone (VI).—A solution of 2.00 g. of III in 50 ml. of 6 *N* hydrochloric acid was boiled under reflux for one hour. After the solution has been neutralized in the cold with solid potassium carbonate, the solid which separated was removed by filtration, and sublimed at 120° under 1 mm. pressure. This gave 0.48 g. (32%) of light yellow crystals, m.p. 117–118°.

Anal. Calcd. for $C_{12}H_{11}NO_3$: C, 66.35; H, 5.10. Found: C, 66.28; H, 5.04.

1-Carbomethoxy-3-carbethoxy-4-quinolizone (IV).—This was prepared from methyl 2-pyridylacetate and diethyl ethoxymethylenemalonate in the same fashion as described for the preparation of III. From 15.1 g. of methyl 2-pyridyl acetate there was obtained 7.0 g. (26%) of blue-tinged, yellow needles, m.p. 159–160°.

Anal. Calcd. for $C_{14}H_{13}NO_5$: C, 61.09; H, 4.76. Found: C, 61.03; H, 4.66.

1-Carbomethoxy-3-carboxy-4-quinolizone.—When a solution of 1.00 g. of IV in 10 ml. of concentrated hydrochloric acid was boiled under reflux, a heavy yellow precipitate separated after about ten minutes heating. If at this point the solution was cooled and the precipitate removed, there resulted 0.89 g. (99%) of product which, after crystallization from ethanol, gave yellow crystals melting at 210–215° with slow decomposition beginning at 185°. On further heating with hydrochloric acid, this product evolved carbon dioxide and was converted to VII.

Anal. Calcd. for $C_{12}H_9NO_5$: C, 58.30; H, 3.67. Found: C, 58.69; H, 3.59.

1-Carbomethoxy-4-quinolizone (VII).—A solution of 1.00 g. of IV in 10 ml. of concentrated hydrochloric acid was boiled under reflux until the precipitate, which separated during the first ten minutes, had just redissolved. The solution was then cooled, neutralized with solid potassium carbonate, and the precipitate, which separated, was removed by filtration. Recrystallization of the crude product from acetone gave 0.62 g. (80%) of yellow needles, m.p. 162–163°. Although Diels and Alder had at one time assigned structure VII to one of the degradation products obtained in their work,[17] this claim was later retracted[18] and, as would be expected, their product (m.p. 148–149°) differs from ours.

Anal. Calcd. for $C_{11}H_9NO_3$: C, 65.02; H, 4.44. Found: C, 65.20; H, 4.22.

4-Quinolizone-1-carbohydrazide.—A mixture of 0.5 g. of 1-carbomethoxy-4-quinolizone (VII) in 5 ml. of hydrazine hydrate (85%) was boiled under reflux until solution was complete. The solution was then allowed to cool, and the crystals, which separated, were removed by filtration. The crude product was recrystallized from water, yielding yellow crystals, m.p. 230–240° (dec.). When the above procedure was repeated using VI instead of VII, a product identical in

(11) K. Winterfield and F. W. Holschneider, *Ber.*, **64**, 137 (1931).

(12) Microanalyses by Mrs. G. Sauvage, Miss C. King, and the Micro-Tech Laboratories.

(13) R. B. Woodward and E. C. Kornfeld, *Org. Syntheses*, **29**, 44 (1949).

(14) W. E. Parham and L. J. Reed, *ibid.*, **28**, 60 (1948).

(15) H. M. Randall, R. G. Fowler, N. Fuson and J. R. Dangl, "Infrared Determination of Organic Structures," D. Van Nostrand Co., New York, N. Y., 1949, p. 26.

(16) V. Boekelheide and S. Rothchild, THIS JOURNAL, **71**, 879 (1949).

(17) O. Diels and K. Alder, *Ann.*, **505**, 136 (1933).

(18) O. Diels and H. Schrum, *ibid.*, **530**, 68 (1937).

appearance and decomposition point resulted. Furthermore, cross-seeding of supersaturated solutions of the two samples induced crystallization in each case and thus it can be assumed that VI and VII are esters derived from the same acid.

Anal. Calcd. for $C_{10}H_9N_3O_2$: C, 59.11; H, 4.46. Found: C, 59.13; H, 4.72.

1-Carbomethoxy-6,7,8,9-tetrahydro-4-quinolizone (IX).—A mixture containing 2.0 g. of 1-carbomethoxy-4-quinolizone, 50 mg. of prereduced Adams catalyst, 50 ml. of alcohol and 5 ml. of concentrated hydrochloric acid was subjected to hydrogenation at room temperature and under atmospheric pressure of hydrogen. Hydrogen uptake stopped after two molar equivalents of hydrogen had been absorbed (about four hours). After removal of the catalyst and solvent, the residue was taken up in warm water and neutralized with potassium carbonate. The solution, on cooling, deposited clusters of crystals which after recrystallization from water yielded 1.6 g. (79%) of white needles, m.p. 139–140°.

Anal. Calcd. for $C_{11}H_{13}NO_3$: C, 63.75; H, 6.32; N, 6.76. Found: C, 63.93; H, 6.63; N, 6.82.

1-Carbomethoxy-4-quinolizidone (X).—A mixture of 1.00 g. of IX and 50 mg. of prereduced Adams catalyst in 50 ml. of ethanol was subjected to hydrogenation at room temperature under atmospheric pressure of hydrogen. Two molar equivalents of hydrogen were absorbed in the course of several hours. After removal of the catalyst and solvent, the residue was sublimed yielding 1.00 g. (98%) of white crystals, m.p. 70–71°.

Anal. Calcd. for $C_{11}H_{17}NO_3$: C, 62.53; H, 8.11. Found: C, 62.78; H, 8.54.

3-Carbomethoxy-4-quinolizidone.—As further evidence that the structure assigned to X was correct, we prepared a sample of 3-carbomethoxy-4-quinolizidone for comparison. This was accomplished by dissolving a sample (2.0 g.) of 3-carbethoxy-4-quinolizidone[16] in methanolic hydrogen chloride and allowing the solution to stand for four days. After removal of the solvent, the residue was neutralized with aqueous sodium carbonate solution and the organic material was extracted with ether. The ether was removed and the residue was subjected to a molecular-type distillation by heating at 100° under 3 mm. pressure. A colorless oil resulted which could not be induced to crystallize by seeding it with X.

Anal. Calcd. for $C_{11}H_{17}NO_3$: C, 62.53; H, 8.11. Found: C, 62.21; H, 8.39.

1-Hydroxymethylquinolizidine (XII).—The reduction of 1-carbomethoxy-4-quinolizidone to 1-carbomethoxyquinolizidine (XI) was carried out by the procedure of Galinovsky and Stern.[19] A mixture of 500 mg. of X, 200 mg. of Adams catalyst and 2 ml. of concentrated hydrochloric acid in 25 ml. of water was subjected to hydrogenation at room temperature and under atmospheric pressure of hydrogen. At the end of 72 hours, two molar equivalents of hydrogen had been absorbed. The catalyst was removed; the solution was neutralized with potassium carbonate, extracted with ether and dried over Drierite. After removal of the ether, the residual oil was distilled in a molecular-still type apparatus by heating at 100° under 3 mm. pressure. The resulting colorless oil, although slightly impure as indicated by analysis (*Anal.* Calcd. for $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71. Found: C, 65.75; H, 9.67.), was employed directly in the next step.

A solution of 150 mg. of XI in 20 ml. of anhydrous ether was added dropwise with stirring to 50 ml. of a 0.05 *M* ethereal solution of lithium aluminum hydride. The reaction mixture was boiled under reflux for four hours, and the excess reagent was then decomposed by addition of moist ether. Sufficient dilute hydrochloric acid was then added to dissolve the precipitated alumina and the aqueous layer was separated and added with cooling to an excess of a 35% solution of potassium hydroxide. The basic solution was extracted with ether, the ethereal solution was dried, and the ether was removed. Sublimation of the residue gave 60 mg. of a colorless oil which quickly formed thick crystals, m.p. 54–57°. After recrystallization from pentane there resulted white crystals, m.p. 57–58° (lit.,[9] 59°).

Anal. Calcd. for $C_{10}H_{19}NO$: C, 70.96; H, 11.31. Found: C, 70.29; H, 11.49.

The identity of XII with *d,l*-lupinine was demonstrated by the agreement in melting point of the following derivatives with those recorded for *d,l*-lupinine: picrolonate, m.p. 203–204° (lit.,[9] 203°); picrate, m.p. 124–125° (lit.,[9] 127°); and methiodide, m.p. 298–301° (dec.) (lit.,[9] 303° (dec.)).

(19) F. Galinovsky and E. Stern, *Ber.*, **76**, 1034 (1943).

ROCHESTER, NEW YORK RECEIVED MARCH 2, 1951

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

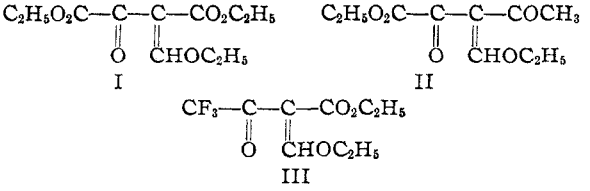
The Synthesis of Ethyl Ethoxymethyleneoxalacetate and Related Compounds

BY REUBEN G. JONES

The condensation of ethyl oxalacetate with ethyl orthoformate in the presence of acetic anhydride has been found to take place readily to yield ethyl ethoxymethyleneoxalacetate. Ethyl ethoxymethyleneacetylpyruvate and ethyl ethoxymethylenetrifluoroacetoacetate have been prepared similarly by reactions of ethyl orthoformate with ethyl acetylpyruvate and ethyl trifluoroacetoacetate, respectively. Some observations have been made on the mechanism of these reactions. Ethyl aminomethyleneoxalacetate and ethyl hydroxymethyleneoxalacetate have been synthesized.

Ethyl ethoxymethyleneoxalacetate (I) was envisioned as a desirable intermediate for the synthesis of certain pyridine and other heterocyclic nitrogen compounds. This compound, I, has been prepared in excellent yields by the condensation of ethyl oxalacetate with ethyl orthoformate and acetic anhydride. Optimum conditions have been determined for carrying out the condensation and some observations have been made on the mechanism of the reaction. In addition, the condensations of ethyl orthoformate and acetic anhydride with ethyl acetylpyruvate and with ethyl trifluoroacetoacetate have been carried out to yield ethyl ethoxymethyleneacetylpyruvate II and ethyl ethoxymethylenetrifluoroacetoacetate III, respectively.

The reaction of ethyl orthoformate and acetic anhydride with active methylene compounds was



first reported by Claisen who prepared ethyl ethoxymethyleneacetoacetate,[1] ethoxymethyleneacetylacetone,[1] and ethoxymethylenemalonic ester.[1] In the latter preparation zinc chloride was used as catalyst.[1,2] Other investigators have reported condensations of ethyl orthoformate and acetic anhydride with ethyl acetonedicarboxylate,[3]

(1) Claisen, *Ber.*, **26**, 2729 (1893); *Ann.*, **297**, 1 (1897).
(2) Wheeler and Johns, *Am. Chem. J.*, **40**, 237 (1908).
(3) Errera, *Ber.*, **31**, 1682 (1898).