INDOLE DERIVATIVES

LXXIII.* REFORMATSKII REACTION IN A NUMBER OF 4-OXO-4,5,6,7-TETRAHYDROINDOLE DERIVATIVES

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(4,5,6,7-Tetrahydro-4-indolidene)acetic acid derivatives were obtained by the reaction of 1-benzyl- and 1-acetyl-4-oxo-4,5,6,7-tetrahydroindoles with the ethyl ester, nitrile, and diethylamide of bromoacetic acid.

4-Oxo-4,5,6,7-tetrahydroindoles, which have become accessible in recent years [2,3], are an interesting subject for study for the preparation of hard-to-obtain 4-hydroxyindoles [4] and for the synthesis of pharmacologically active compounds [5,6].

We have carried out the Reformatskii reaction for 4-oxo-4,5,6,7-tetrahydroindole (I) and its derivatives (II and III) with bromoacetic acid derivatives in order to obtain 4-alkyltetrahydroindoles. The reaction was carried out with excess Reformatskii reagent (no less than 2 moles per mole of carbonyl compound) in tetrahydrofuran with mercuric chloride-activated zinc filings [7].

The starting ketone was recovered quantitatively in the attempted reaction of I [2] with ethyl bromoacetate or N,N-diethylbromoacetamide. The reduced reactivity of the carbonyl group with respect to nucleophilic attack by the $\overline{C}H_2COR$ anion [8] is probably due to the effect of the unshared pair of electrons of nitrogen, which is transmitted through the conjugation chain. The Reformatskii reaction was possible for the N-acetyl derivative (II) of I, in which this effect is weakened. The reaction of II with the ethyl ester or diethylamide (VII) of (4,5,6,7-tetrahydro-4-indolidene)acetic acid. The reaction of the ethyl ester, nitrile, and diethylamide of bromoacetic acid with the N-benzyl derivative (III) of I also gave the corresponding benzyl derivatives (V, VI, and VIII, respectively) of (4,5,6,7-tetrahydro-4-indolidene)acetic acid. Ester V was obtained in a yield of only 10% in the reaction of III with the diethyl ester of carboxymethylphosphinic acid (the Horner reaction) [9]. The presence of ester, nitrile, and amide groups in IV-VIII is confirmed by the IR spectral data. The absence of an absorption band at 3000-3600 cm^{-1} is evidence that V, VI, and VIII do not have hydroxyl groups. (The bands at 3320 cm^{-1} for IV and at 3200 cm^{-1} for VII are due to the NH groups.) Compounds IV-VIII are consequently not β-hydroxy compounds – the direct products of the Reformatskii reaction – but are formed as a result of dehydration of the β-hydroxy compounds, which proceeds extremely readily under the reaction conditions and is due to the formation of a system of conjugated double bonds. The position of the double bond in the indicated compounds was established by means of the PMR spectra. The vinyl protons in the PMR spectra of IV, V, and VIII have singlet signals at 5.8-6.1 ppm, while the vinyl protons in the alternative structures of IX should have multiplet signals in this region. There are three groups of signals at 1.7-3.1 ppm, which correspond to the CH_2 groups in the 5-, 6-, and 7-positions. Compounds IV-VIII have UV spectra that are similar in character and absorption intensity. The conjugation pointed out above should probably also explain the fact that the nucleophilic reactions of the ester group are hindered. Thus saponification of ester V to acid X proceeds under rather severe conditions, while the replacement of the ester group by amide and hydrazide groups does not occur on heating with ammonia in an

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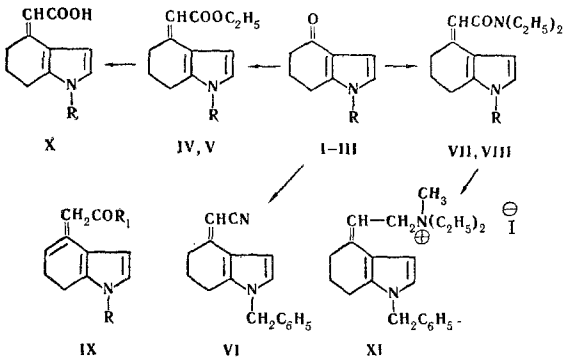
autoclave and on refluxing with hydrazine hydrate at high temperatures. The same behavior with hydrazine hydrate was noted for substituted pyrryl-3-acrylic acids [10]. The reduction of diethylamide VIII by lithium aluminum hydride gives an amine, which was characterized as the methiodide (XI).



I R=H; II R=COCH$_3$; III R=CH$_2$C$_6$H$_5$; IV R=H; V R=CH$_2$C$_6$H$_5$; VII R=H; VIII R=CH$_2$C$_6$H$_5$

EXPERIMENTAL

The IR spectra of mineral oil suspensions were recorded with a UR-10 spectrometer. The UV spectra of ethanol solutions were obtained with an EPS-3 spectrometer, and the PMR spectra of deuterochloroform solutions were recorded with a JNM-4H-100 spectrometer (100 MHz) with tetramethylsilane as the internal standard. The chromatography was carried out in a thin layer of RUF-254 Silufol with a chloroform–acetone (9:1) system (unless otherwise specified) with development by the Erlich reagent at 100 deg. The R_f values (the spot color is given in parentheses) are indicated for a solvent range of 11 cm. Preparative chromatography was realized on KSK silica gel. Prior to vacuum evaporation, the solutions were washed with water until they were neutral and dried with anhydrous sodium sulfate.

1-Acetyl-4-oxo-4,5,6,7-tetrahydroindole (II). A 3.73 g (0.095 g-atom) sample of potassium was dissolved at 50–55 deg in dry tert-butyl alcohol, and 200 ml of dry benzene was added by drops with simultaneous removal of the excess alcohol by distillation. The boiling point of the solution rose from 73 to 78 deg. A 10 g (0.074 mole) sample of I [2] was added to the resulting suspension, and the mixture was refluxed for 2 h, cooled to room temperature, and 7.5 g (0.095 mole) of acetyl chloride was added by drops. The mixture was stirred for 30 min, and the solution was washed with 10% sodium bicarbonate until it gave a neutral reaction. The solvent was removed by distillation to dryness, and the residue was recrystallized from cyclohexane to give 8.8 g (67%) of II with mp 97–98 deg. Found: C 67.9; H 6.2; N 8.1%. $C_{12}H_{13}NO_3$. Calculated: C 67.8; H 6.3; N 7.9%. IR spectrum, cm^{-1}: 1730 (C=O), 1660 (amide C=O).

General Methods for Performing the Reformatskii Reaction. A) A solution of 0.025 mole of ketone II or III and 0.05 mole of ethyl bromoacetate in 100 ml of dry tetrahydrofuran was added in the course of 30 min to 0.05 g-atom of zinc filings that had been washed with acetone and ether, dried at 100 deg, and activated by several mercuric chloride crystals. The mixture was refluxed for 10–12 h, the solution was cooled to 0 deg, and 10% aqueous acetic acid was added with stirring. The reaction product was extracted with benzene or methylene chloride, and the extract was evaporated to dryness.

B) Zinc filings (0.18 g-atom) and a solution of 0.18 mole of N,N-diethylbromoacetamide [11] or bromoacetonitrile [12] in dry tetrahydrofuran were added in three identical portions, each after 1 h of refluxing, to a solution of 0.056 mole of ketone II or III in dry tetrahydrofuran containing several mercuric chloride crystals. The mixture was refluxed for 7 h and worked up as indicated in method A.

Ethyl (4,5,6,7-Tetrahydro-4-indolidene)acetate (IV). A total of 3.5 g of an oil was obtained from 3.25 g of II by method A after evaporation. The oil was dissolved in 25 ml of 2% potassium hydroxide in methanol and allowed to stand at room temperature for 30 min. The solution was neutralized with acetic acid, the solvent was removed by distillation to dryness, and the residue was washed with water. The crystalline residue was triturated with benzene, and 0.99 g of I with R_f 0.23 (rose) and mp 184–186 deg (from methanol) was filtered off. The benzene mother liquor was passed through a layer of silical gel containing carbon to give 2.24 g (45%) of IV with mp 120–123.5 deg (from cyclohexane, 70% aqueous methanol) and R_f 0.8 (violet).

Found: C 70.3; H 7.3; N 7.3%. $C_{12}H_{15}NO_2$. Calculated: C 70.3; H 7.4; N 6.8%. IR spectrum, cm^{-1}: 3320 (NH), 1675 (ester CO). UV spectrum: λ_{max} 320 nm, log ε 4.35. PMR spectrum: 1.93 multiplet, 2.67 triplet, 3.11 triplet ($3CH_2$), 5.95 singlet (CH=C), 6.35 multiplet, $J_{1,2}$ = 2.4 Hz (β-CH), 6.63 triplet, $J_{1,3}$ =2.1 Hz (α-CH).

Ethyl (1-Benzyl-4,5,6,7-tetrahydro-4-indolidene)acetate (V). A) A total of 18.7 g of an oil was obtained from 15 g of III by method A. This oil was dissolved in cyclohexane–methylene chloride (6:1), and the solution was passed twice through a layer of silica gel to give 10.2 g (51%) of V with mp 90-92.5 deg (from cyclohexane, methanol) and R_f 0.82 [dark-blue, cyclohexane–acetone (7:3)]. Found: C 77.6; H 7.0; N 4.7%. $C_{19}H_{21}NO_2$. Calculated: C 77.3; H 7.2; N 4.7%. IR spectrum, cm^{-1}: 1690 (ester C=O), 1610 (conjugated C=C). UV spectrum: λ_{max} 318 nm, log ε 4.42. PMR spectrum, δ, ppm: 1.21 triplet, 4.09 quartet (CH_3CH_2), 1.78 multiplet, 2.43 triplet, 3.01 triplet ($3CH_2$), 4.86 singlet, 7.0 multiplet ($CH_2C_6H_5$), 5.86 singlet (CH=C), 6.27 doublet (β-CH), 6.50 doublet (α-CH).

B) A solution of sodium ethoxide (from 0.22 g of sodium and 8 ml of alcohol) was added at room temperature in the course of 15 min to 0.5 g (0.0025 mole) of III in 7 ml of dry tetrahydrofuran. A solution of 2.12 g (0.0107 mole) of the diethyl ester of carboxymethylphosphinic acid in 7 ml of dry tetrahydrofuran was then added by drops in the course of 15 min. The mixture was refluxed for 5 h, and a freshly prepared portion of the sodium derivative from 1.06 g of the diethyl ester of carbethoxymethylphosphinic acid and 0.11 g of sodium in 4 ml of diethyl ether was added. The reaction mixture was again refluxed for another 2 h and evaporated to dryness. The reaction product was extracted with benzene, and the extract was evaporated to dryness to give 0.45 g of an oil (R_f 0.62, 0.82) [cyclohexane–acetone (7:3)], which was chromatographed with a column filled with 10 g of silica gel. Elution with 100 ml of methylene chloride gave 0.07 g (10%) of V with mp 89-90 deg. Further elution with 200 ml of methylene chloride–chloroform (1:1) gave 0.35 g of III with R_f 0.62 (raspberry-colored).

(1-Benzyl-4,5,6,7-tetrahydro-4-indolidene)acetic acid (IX). A mixture of 0.5 g of V in 30 ml of 10% methanolic potassium hydroxide was refluxed for 6 h, and the solution was neutralized with acetic acid and diluted with 30 ml of water. The resulting precipitate was filtered and crystallized twice from methanol to give 0.16 g of IX with mp 159-161 deg. Found: C 76.3; H 6.2; N 5.6%. $C_{17}H_{17}NO_2$. Calculated: C 76.4; H 6.4; N 5.2%. IR spectrum, cm^{-1}: 2550-2750 (OH), 1670 (CO). UV spectrum: λ_{max} 297 nm, log ε 4.25.

(1-Benzyl-4,5,6,7-tetrahydro-4-indolidene)acetonitrile (VI). A total of 7.1 g of an oil was obtained from 6 g of III by method B. This oil was dissolved in benzene–cyclohexane and passed through a layer of silica gel. Benzene–cyclohexane (1:1), followed by benzene, eluted 4.65 g of an oil that was rechromatographed with a column filled with 70 g of silical gel. A total of 300 ml of benzene–methylene chloride (3:1) eluted 2.22 g (36%) of an oil with R_f 0.61 [blue, cyclohexane–acetone (7:3)], while 200 ml of the same mixture eluted 1.51 g of III. A 2.22 sample of the oil was rechromatographed with a column filled with 90 g of aluminum oxide. Benzene eluted 1.12 g of a light-yellow oil, which, after trituration with cyclohexane, gave 0.83 g of VI with mp 49-53 deg. Found: C 81.9; H 6.5; N 11.3%. $C_{17}H_{16}N_2$. Calculated: C 82.2; H 6.5; N 11.3%. IR spectrum, cm^{-1}: 2200 (C≡N), 1590 (conjugated C=C).

N,N-Diethyl(4,5,6,7-tetrahydro-4-indolidene)acetamide (VII). A total of 16 g of an oil was obtained from 1.27 g of II via method B. This oil was refluxed for 30 min with 12 ml of 2% methanolic potassium hydroxide, and the solution was neutralized with acetic acid and evaporated to dryness. The residue was washed with water and triturated with acetone to give 0.5 g (50%) of VII with mp 133.5-135.5 deg (from ethyl acetate–hexane) and R_f 0.28 (violet). Found: C 72.0; H 8.7; N 12.3%. $C_{14}H_{20}N_2O$. Calculated: C 72.4; H 8.7; N 12.1%. IR spectrum, cm^{-1}: 3120-3200 (NH), 1615 (amide CO). UV spectrum: λ_{max} 312 nm, log ε 4.19.

N,N-Diethyl(1-benzyl-4,5,6,7-tetrahydro-4-indolidene)acetamide (VIII). A total of 16 g of oil was obtained from 12.7 g of III via method B. This oil was triturated in ethyl acetate–petroleum ether, and the solid was separated by filtration to give 9.98 g (55%) of VIII with mp 107-108 deg (from aqueous methanol) and R_f 0.66 (violet). Found: C 78.6; H 8.0; N 9.1%. $C_{21}H_{26}NO_2$. Calculated: C 78.2; H 8.1; N 8.7%. IR spectrum: 1620 cm^{-1} (amide CO). UV spectrum: λ_{max} 308 nm, log ε 4.28. PMR spectrum: 1.13 triplet, 3.37 quartet ($2CH_2CH_3$), 1.08 multiplet, 2.45 triplet, 2.87 triplet ($3CH_2$), 4.97 singlet, 6.96 multiplet ($CH_2C_6H_5$), 6.08 (CH=C), 6.29 triplet (β-CH), 6.96 singlet (α-CH).

4-Diethylaminoethylidene-1-benzyl-4,5,6,7-tetrahydroindoline Methiodide (X). A solution of 0.5 g (0.0015 mole) of VIII in 50 ml of dry tetrahydrofuran was added with stirring at room temperature to a suspension of 0.5 g (0.013 mole) of $LiAlH_4$ in 20 ml of dry tetrahydrofuran, and the mixture was stirred for

3.5 h until VIII vanished completely (as monitored by paper chromatography). Water (0.5 ml) was added at +5 deg, and the resulting precipitate was filtered and washed with tetrahydrofuran. The solution was evaporated to dryness, 0.49 g of the residual oil was dissolved in 25 ml of dry ether, and 2 g of freshly distilled methyl iodide in 20 ml of ether was added to give 0.36 g (52%) of X. The product decomposed on heating. Found: C 58.3; H 6.7; I 27.9; N 6.2%. $C_{22}H_{31}IN_2$. Calculated: C 58.6; H 6.9; I 28.2; N 6.2%. IR spectrum: 1640 cm^{-1} (conjugated C=C).

LITERATURE CITED

1. O. D. Shalygina, L. Kh. Vinograd, and N. N. Suvorov, Khim. Geterotsikl. Soedin., 1062 (1971).
2. H. Stetter and R. Lauterbach, Ann., 655, 21 (1962).
3. A. N. Kost, L. G. Ovseneva, and T. G. Shuvaeva, Khim. Geterotsikl. Soedin., 717 (1966).
4. S. Hauptmann, H. Blume, H. D. Hartmann, and P. Franke, Z. Chem., 6, 183 (1966).
5. A. Lugermann and J. Herrmann, Clin. Pharm. Ther., 8, 261 (1967).
6. W. A. Remers, P. N. James, and M. J. Weiss, J. Org. Chem., 28, 1169 (1963).
7. R. E. Miller and F. F. Nord, J. Org. Chem., 16, 728 (1951).
8. L. H. Klemm and G. M. Bower, J. Org. Chem., 23, 344 (1958).
9. L. Horner, Ber., 95, 581 (1962).
10. H. Fischer, O. Süs, and F. Weilguny, Ann., 481, 169 (1930).
11. N. L. Drake, C. M. Eaker, and W. Shenk, J. Am. Chem. Soc., 70, 677 (1948).
12. W. Steinkopf, Ber., 38, 2694 (1905).