# DERIVATIVES OF TETRAHYDROINDOLE

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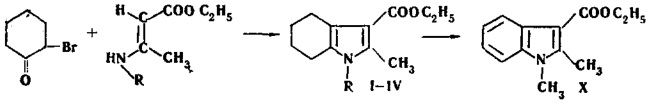
Khimiya Geterotsiklicheskikh Soedinenii, Vol. 4, No. 1, pp. 137–139, 1968

UDC 547.753'754:542.953:543.422.4

With the aim of synthesizing structural analogs of dimecarbene and of other highly-effective hypotensive indole derivatives, the synthesis of a series of esters of tetrahydroindole-3-carbonic acids was achieved by condensing α-bromocyclohexanone with β-aminocrotonic ester and with β-aminocrotonic esters substituted at the nitrogen. Hydrolysis of tetrahydroindole-3-carbonic acids esters by fusion with potassium hydroxide yielded a series of tetrahydroindole-3-carbonic acids. Dehydrogenation of 1, 2-dimethyl-3-carboethoxy-4, 5, 6, 7-tetrahydroindole on reduced nickel yielded 1, 2-dimethyl-3-carboethoxyindole, and hydrolysis of the latter yielded 1, 2-dimethylindole-3-carbonic acid.

We had obtained a series of indole derivatives with high hypotensive activity [1]. In order to elucidate the relation between the structure of the substances obtained and their biological activity, and with the aim of revealing the structural elements of the molecule responsible for the hypotensive effect, we have presented in this work the results of the synthesis of tetrahydroindole derivatives. These latter compounds have the same structural fragment common to dimecarbene and to other indoles, which were thoroughly investigated by Shadurskii and coworkers [1]. One of the tetrahydroindole derivatives, the 2-methyl-3-carboethoxy-4,5,6,7-tetrahydroindole (I), was obtained by condensing chlorocyclohexanone with acetoacetic ester and ammonia [2]. We succeeded in synthesizing a series of tetrahydroindoles (I–IV) by condensing α-bromocyclohexanone with β-aminocrotonic ester and with β-aminocrotonic esters substituted at the nitrogen. The reaction of β-aminocrotonic esters with α-bromocyclohexanone proceeds by heating the reactants for a short time in absolute alcohol in the presence of potassium carbonate. As is known, the esters of tetrahydroindole-3-carbonic acids are hydrolyzed to the corresponding carbonic acids by prolonged heating with alcoholic alkali only [3], by which a low yield of acids is obtained. We succeeded in hydrolyzing the esters of tetrahydroindole carbonic acids I–IV by fusion with potassium hydroxide at 170°–210° C. We obtained a series of tetrahydroindole-3 carbonic acids (V–IX) with a yield of 75–95%. 1-Phenyl- and 1-(p-toyl) 2-methyl-4, 5, 6, 7-tetrahydroindole- 3-carbonic acids (VI, VIII) were synthesized by hydrolyzing the corresponding esters, which we were not able to separate in pure form.

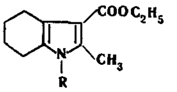
In view of the wide availability of tetrahydroindoles, there is evident interest in transforming them into the corresponding indole derivatives by dehydrogenation. By dehydrogenating 1,2-dimethyl-3-carboethoxy-4,5,6,7-tetrahydroindole (II) on reduced nickel under the conditions for the dehydrogenation of tetrahydrocarbazole [4], we obtained 1,2-dimethyl-3-carboethoxyindole (X), which had been previously prepared by another method [5]. Hydrolysis of ester X leads to the known 1,2-dimethylindole-3-carbonic acid (XI). Yet, under the same conditions, we were not able to dehydrogenate other tetrahydroindole derivatives (I, III, IV), probably due to peculiarities in their structure.



I R = H; II R = $CH_3$; III R = $CH_2C_6H_5$; IV R = n-$C_4H_9$

The structure of indole derivative X is confirmed by revealing in its IR spectrum bands at 3070 $cm^{-1}$ and intensive absorption bands at 747 and 756 $cm^{-1}$, which warrants assuming the presence of an aromatic group with four adjacent hydrogens (o-substituted benzene ring) [6]. A comparison of the UV spectra of the tetrahydroindole derivatives obtained (I–IV), of the indole derivative X, and of 1,2-dimethyl-3-carboethoxy-5-methoxyindole (XI) [7] shows that the transition of tetrahydroindoles to indoles is associated with an increase in the intensity of the absorption bands and their displacement to a longer wavelengths

Table 1



| Compound | R | Bp., °C (pressure, mm) | Empirical formula | Found, % |  |  | Calculated, % |  |  | Yield, % |
|---|---|---|---|---|---|---|---|---|---|---|
|  |  |  |  | C | H | N | C | H | N |  |
| I | H | * | — | — | — | — | — | — | — | 37 |
| III | $C_6H_5CH_2$ | 200—205 (2) | $C_{19}H_{23}NO_2$ | 76.40<br>76.41 | 7.51<br>7.41 | 5.10<br>5.05 | 76.74 | 7.80 | 4.71 | 30 |
| IV | n-$C_4H_9$ | 165—170 (2) | $C_{16}H_{25}NO_2$ | 72.59<br>72.54 | 9.16<br>9.27 | 5.20<br>5.45 | 72.97 | 9.57 | 5.32 | 40 |

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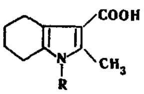
*Mp. 132–133°; according to literature data, mp. 132°.

Table 2



| Compound | R | Mp., ° C | Empirical formula | Found, % |  |  | Calculated, % |  |  | Yield, % |
|---|---|---|---|---|---|---|---|---|---|---|
|  |  |  |  | C | H | N | C | H | N |  |
| VI | $C_6H_5$ | 245—246 | $C_{16}H_{17}NO_2$ | 75.51<br>76.50 | 6.98<br>6.87 | 5.38<br>5.16 | 75.27 | 6.71 | 5.49 | 95 |
| VII | $C_6H_5CH_2$ | 214—215 | $C_{17}H_{19}NO_2$ | 76.10<br>75.84 | 7.10<br>7.06 | 5.16<br>5.20 | 75.81 | 7.11 | 5.20 | 94 |
| VIII | *p*-$CH_3C_6H_4$ | 244—245 | $C_{17}H_{19}NO_2$ | 75.40<br>75.40 | 6.99<br>7.18 | 5.04<br>5.02 | 75.81 | 7.11 | 5.20 | 53 |
| IX | *n*-$C_4H_9$ | 176—177 | $C_{14}H_{21}NO_2$ | 71.75<br>71.72 | 8.80<br>8.55 | 6.14<br>6.04 | 71.46 | 8.99 | 5.95 | 76 |

region. Analogous changes, although in a lesser degree, are observed in the UV spectra of tetrahydroindole derivatives by substituting the hydrogen bound to the nitrogen of the pyrrole ring by alkyl or aryl groups. As in the case of the esters of substituted indole-3-carbonic acids [8], the IR spectra of the esters of tetrahydroindole carbonic acids reveal a significant decrease in the carbonyl frequency (1665–1695 cm$^{-1}$). It is interesting to note that neither the aromatization of the six-membered ring II by transforming it to X, nor the character of the substituent at the nitrogen atom of the pyrrole ring exert appreciable influence on the position of the carbonyl-absorption bands. Thus, in the IR spectra of II, X, and XI intensive bands at 1695, 1696, and 1697 cm$^{-1}$ respectively are observed. Tetrahydroindoles II-IV, which are substituted at the nitrogen atom, absorb at 1690–1697 cm$^{-1}$, independent of the character of the substituent; but derivative I, which is not substituted at the nitrogen atom, exhibits a significant decrease in the carbonyl frequency to 1665 cm$^{-1}$. The transition from esters to acids also leads to a sharp displacement of the carbonyl absorption band in the 1650–1665 cm$^{-1}$ region.

## EXPERIMENTAL

**1,2-Dimethyl-3-carboethoxy-4,5,6,7-tetrahydroindole (II).** To a solution of 24 g (0.13 mole) of α-bromocyclohexanone in 100 ml of absolute alcohol 30 g of fused potassium carbonate was added, and then at once 15 g (0.1 mole) of N-methyl-β-aminocrotonic ester. The reaction mixture was heated for 2 hr on a steam bath. The solid salt precipitate was separated from the filtrate, the alcohol was distilled off under vacuum, and the volatile compounds were distilled off with steam. The residue solidified upon the addition of 50% methanol. Yield 7.59 g (33%) II, mp, 47°–47.5°C (ex MeOH)*. Found, %: C 70.13; 70.35; H 8.70; 8.40; N 6.28; 6.40%. Calculated for $C_{13}H_{19}NO_2$: C 70.56; H 8.65; N 6.33%.

In an analogous way, tetrahydroindoles I, III, and IV (Table 1) were obtained from equimolecular quantities of α-bromocyclohexanone and β-aminocrotonic ester, and its N-benzyl- or its N-n-butyl derivative.

**1,2-Dimethyl-4,5,6,7-tetrahydroindole-3-carbonic acid (V).** To a solution of 5.6 g (0.1 mole) of potassium hydroxide in 1.5 ml of water heated to 170° C 2.2 g (0.01 mole) of II was added with vigorous stirring. The reaction mixture was kept at 170°–210° C for 10 minutes. The solidified reaction mass was then dissolved in water, and the solution filtered. The filtrate was cooled in ice, and acidified to pH 6 with 10% HCl. The crystals which separated out were filtered off and washed on the filter with acetone. Yield of V 1.47 g (77.3%), mp. 245°–246° C (ex acetone). Found,%: C 68.10; 67.96; H 7.67; 7.78; N 7.03; 6.98%. Calculated for $C_{11}H_{15}NO_2$: C 68.37; H 7.82; N 7.25%. Data for other 4,5,6,7-tetrahydroindole-3-carbonic acids (VI-IX) are presented in Table 2.

**1,2-Dimethyl-3-carboethoxyindole (X).** 5 ml of a suspension of reduced nickel in water was added to 60 ml of xylene. The water from this mixture was distilled off in the form of an azeotrope with xylene. To the suspension of the catalyst in xylene 1.4 g (0.006 mole) of ester II was added, and the reaction mixture was boiled for 6 hr. Then the catalyst was separated from the hot solution. The xylene was distilled off from the filtrate under vacuum, and the residue was recrystallized from alcohol. Yield of X 0.73 g (56%), mp. 95°–96° C (ex EtOH). According to literature data [5], mp is 95° C. Found, %: C 71.74; 71.85; H 6.78; 6.92; N 6.32; 6.57%. Calculated for $C_{13}H_{15}NO$ $NO_2$: C 71.87; H 6.96; N 6.45%.

**1,2-Dimethylindole-3-carbonic acid (XI).** 0.5 g (0.01 mole) of potassium hydroxide and 0.31 g (0.001 mole) of ester X were reacted together as previously described. Yield of XI 0.13 g (48%), mp. 204° – 205° C (ex acetone), in a capillary mp. is 191°–192° C (decomp.). According to literature data [5], mp. is 185°C. Found, %: N 7.41 Calculated for $C_{11}H_{11}NO_2$, %: N 7.40.

## REFERENCES

1. E. V. Vinogradova, A. N. Grinev, K. S. Shadurskii, T. Yu, Il'yuchenok, Vestn. AMN SSSR, 1, 69, 1963.
2. A. Treibs, Ann., 524, 285, 1936.
3. A. Treibs and D. Dinalli, Ann., 517, 152, 1935.
4. W. E. Badcock and K. H. Pausaker, J. Chem. Soc., 1373, 1951.
5. J. Degen, Ann. 236, 157, 1886.
6. K. Nakanisi, Infrared Spectra and the Structure of Organic Compounds [in Russian], Moscow, 133, 1965.
7. A. N. Grinev, I. A. Zaitsev, V. I. Shvedov, and A. P. Terent'ev, ZhOKh, 28, 447, 1958.
8. A. N. Grinev, V. I. Shvedov and E. K. Panisheva, ZhOKh, 1, 2051, 1965.

10 February 1966

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*The melting point was in all cases determined in a Koffler box.